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Archives of Internal Medicine

VOLUME 37 JUNE, 1926 NUMBER 6

ARTERIOSCLEROSIS AND INCREASED BLOOD PRESSURE

EXPERIMENTAL PRODUCTION *

FRANKLIN R. NUZUM, M.D.; BEATRICE SEEGAL, M.D.
RUTH GARLAND, M.D.
AND
MARGARET OSBORNE, M.S.
SANTA BARBARA, CALIF.

There is a great diversity of opinion concerning the etiologic factors of increased blood pressure and arteriosclerosis. The frequent association of the two conditions is granted. Which precedes the other, and what precedes both, have been matters of much study and debate. Five theories regarding the etiology of arteriosclerosis and hypertension may be considered:

1. Mechanical-physical theory. A wearing out of the blood vessels as the result of the stress and strain of life.

2. Chemical or infectious poisons theory. These may be exogenous, as from nicotine, or endogenous, as in chronic bacterial infections, diabetes, gout and nephritis.

3. Metabolic theory. Poorly balanced diets with excess of protein or cholesterol; harmful but as yet undesignated end products of protein metabolism.

4. Predisposition of certain groups of persons to degeneration of blood vessels theory.

5. Disturbance of the acid-base balance theory. Such a disturbance in human subjects results from the continued eating of a diet high in protein foods. The urine from such a diet is frequently from 100 to 1,000 times as acid as the body fluids.[1] It has been suggested that the continued passage of an excessively acid urine might in itself damage the kidneys and play some rôle in the production of a generalized arteriosclerosis.

---

* From the laboratories of the Potter Memorial Clinic of the Santa Barbara Cottage Hospital.

1. Sansum, W. D.; Blatherwick, N. R., and Smith, F.: The Use of Basic Diets in the Treatment of Nephritis, J. A. M. A. **81**:883 (Sept. 15) 1923.

In a previous article [2] we have demonstrated the results of feeding experiments with rabbits which resulted in a considerable increase in blood pressure (fig. 1). Varying degrees of arteriosclerosis, in addition to the increase in blood pressure, were produced in three groups of twelve animals on high proten diets. One group was fed an animal protein, liver; a second group, oat protein, and a third group, soy bean protein.

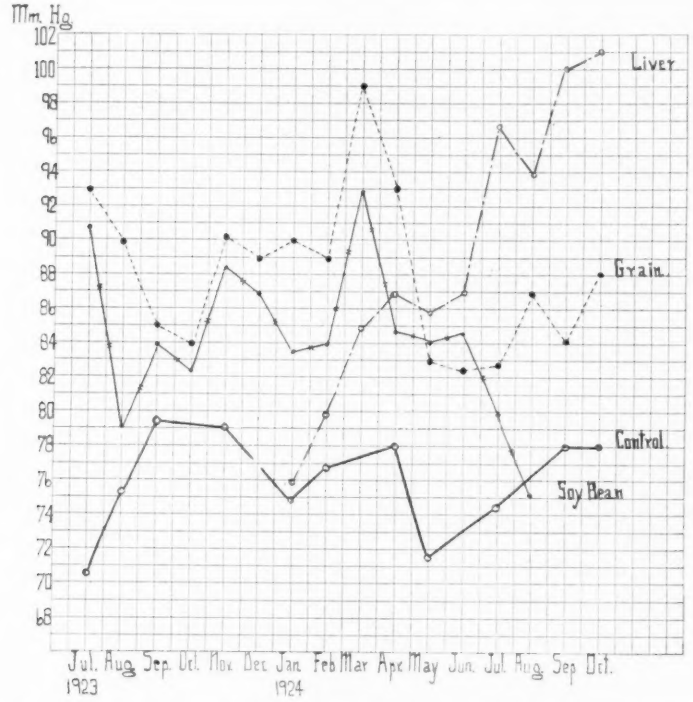

Fig. 1.—Blood pressure in four groups of animals: each dot represents average of readings on the twelve animals in that group.

This article is concerned with the pathologic aspect of this degenerative process, with the gross and microscopic relationship to human sclerosis, and with a consideration of the etiologic factors that may have played a rôle in producing these changes.

OBSERVATIONS

Liver Diet.—The aortas of seven rabbits of a group of ten kept on a liver diet for from three to eleven months presented extensive arterio-

2. Nuzum, F. R.; Osborne, M., and Sansum, W. D.: The Experimental Production of Hypertension, Arch. Int. Med. **35**:492 (April) 1925.

sclerosis. Three rabbits on this diet for a period of less than three months did not present evidence of blood vessel change. Grossly, the intima of the aorta presented raised yellow-white areas which in some instances involved the entire lumen of the vessel and extended in patches from the root to its iliac bifurcation. In one instance the pulmonary artery also was involved. Microscopically, this process of intimal change has been followed from an early swelling of the intercellular cement substance of the intima to a marked thickening with the deposition of calcium soap in considerable amounts. In the later stages of intimal swelling, the elastic fibers become destroyed and the cellular structures are replaced by a homogeneous hyaline-like material. It is in this hyaline

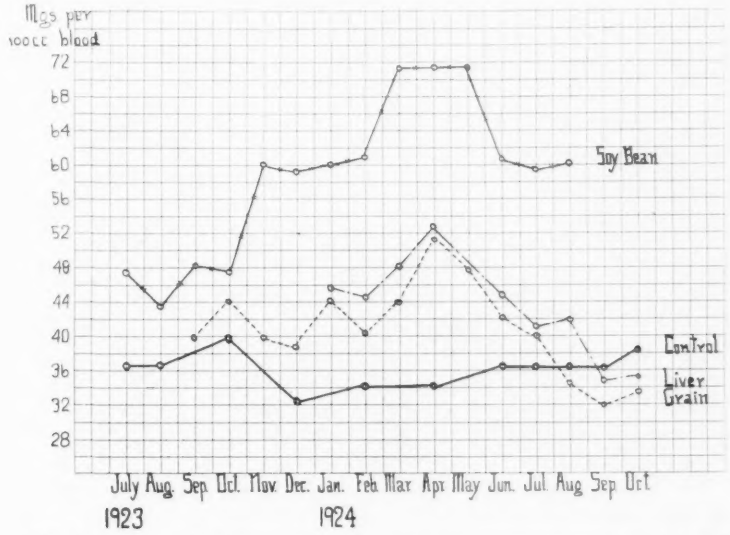

Fig. 2.—Nonprotein nitrogen of blood: each dot represents average of twelve nonprotein nitrogen determinations of that group.

substance that the calcium is found. Not until the intimal changes have reached an advanced stage do the endothelial cells covering the intima break down. In some instances of advanced change in the intima, these degenerative processes have extended by continuity into the media, but never extensively. The intimal changes were particularly prone to occur about the mouths of the coronary and intercostal arteries, that is, at points of stress. In each of the seven liver fed animals in which sclerosis of the aorta was found, sclerosis of one or both coronary arteries was likewise present to a considerable degree. The microscopic picture of the coronary sclerosis was precisely like that of the aorta.

There was no evidence of spontaneous (medial) sclerosis in any animal of the liver group. In spontaneous sclerosis the changes are confined to the media and consist of a necrosis of the smooth muscle cells and of a deposition of calcium in the necrotic areas. The overlying intima is not involved. On the frequency of this condition in rabbits there have been many reports, but nearly all lack a careful study of the histology and the writers have therefore failed to recognize these two types of sclerosis. The literature on this question has recently been summarized by Newburgh and Clarkson.[3]

The blood pressures in this group were higher than in any other and were highest in those animals in which the sclerosis was most marked. In each of these animals there also was definite evidence of kidney

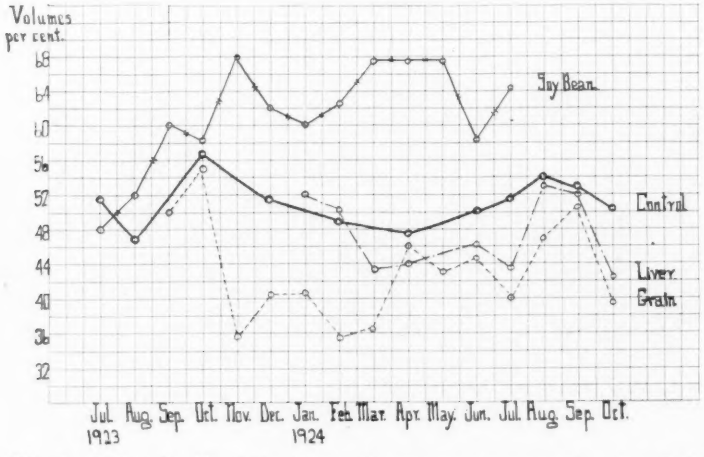

Fig. 3.—Carbon dioxide of blood: each dot represents average of carbon dioxide determinations on blood of the twelve animals in that group.

injury as shown by the presence of albumin and casts in the urine and by an increase of nonprotein nitrogen and urea nitrogen in the blood. The urines of these animals were decidedly acid, the p_H ranging from 5.0 to 7.0. The carbon dioxide of the blood serum was decreased.

Grain Diet.—The aortas of seven of eleven animals kept on an oat diet for two years (with the addition of green vegetables at stated times) presented marked arteriosclerosis. These changes were most pronounced in the arch and extended down into the abdominal aorta as isolated scattered patches. The largest areas of intimal thickening in this group

3. Newburgh, L. H., and Clarkson, Sarah: The Production of Arteriosclerosis in Rabbits by Feeding Diets Rich in Meat, Arch. Int. Med. **31**:653 (May) 1923.

were 10 by 8 mm. and 15 by 3 mm. These patches, as in the liver group, were especially to be found about the mouths of the intercostal vessels. The coronary arteries contained areas of sclerosis in three of the seven instances that presented aortic changes.

Spontaneous or medial sclerosis was present in three of the seven animals that had an intimal sclerosis. This type of change presents grossly a thinning of the wall of the aorta in contrast to a thickening such as occurs in arteriosclerosis. The intima is depressed over these thinned areas but is intact. On section, calcification, confined to the media, is present. This calcification may extend for considerable distances along the vessel. Its width was usually not more than from 3 to 4 mm. In none of our instances was the intima involved.

In one instance a group of cartilage cells was found beneath an area of medial calcification. This has been seen before but seems to be rare.

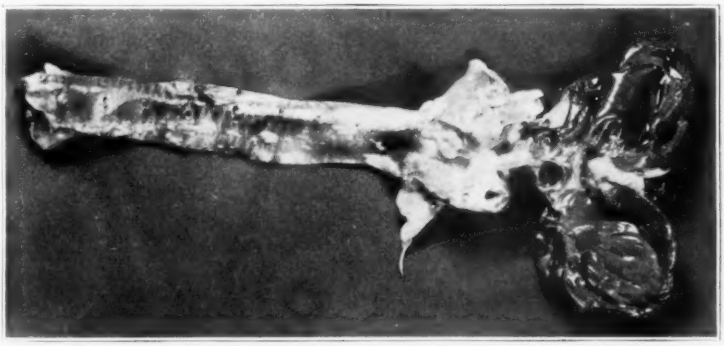

Fig. 4.—Extensive sclerosis of intima of aorta of rabbit that had been on a liver protein diet for fifteen months.

The most pronounced arteriosclerosis was found in the animals that had been on the grain diet for the longest time (two years). It was these animals, also, that had the most marked increase in blood pressure, the maximum pressures ranging between 90 and 100 mm. of mercury, whereas the pressures of these animals at the beginning of the experiment and the pressures of the control animals averaged 74 mm. The kidneys of these grain fed animals that presented areas of sclerosis and increased blood pressure likewise gave evidence of injury. Albumin and casts were present in the urine after the sixth month of the experiment. The urine was acid, the p_H ranging from 6.0 to 6.8. The carbon dioxide of the blood serum was decreased. The nonprotein nitrogen and the urea nitrogen of the blood were increased.

Soy Bean.—A third group of twelve animals was kept on a diet of ground soy beans for two years. (At weekly intervals greens were

added to this diet to prevent deficiency diseases.) The protein in this diet averaged 36 per cent and was of the vegetable type. It was given because it produces an alkaline urine in contrast to the acid urines that the other two groups of protein produce. The p_H of the urine of this soy bean group averaged 9.0, which is high even for the rabbit whose urine on a herbiverous diet does not exceed a p_H of 8.0. Not one of the twelve animals in this group presented true arteriosclerosis. Three presented areas of spontaneous or medial sclerosis. One of the animals presenting this type of sclerosis, which began just above the aortic cusps and spread up over the arch almost totally covering the transverse and descending portions and extending on down along the entire length of the aorta, developed an infected wound of the neck during the thirteenth

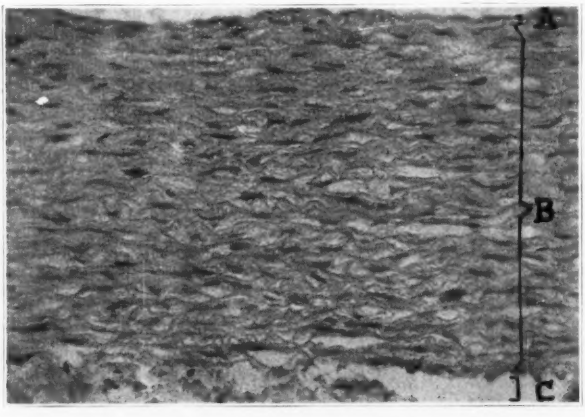

Fig. 5.—Section of normal rabbit aorta: *A*, intima; *B*, media, and *C*, adventitia.

month of the experiment and was killed on the seventeenth month because of its poor condition. The relation of this infection to the medial sclerosis must be considered. The blood pressure of this animal did not exceed 90 mm. of mercury at the maximum. Clinically, the kidneys did not give evidence of damage. There was no increase of the nonprotein nitrogen and the urea nitrogen of the blood.

Controls.—A group of twelve control animals was kept under the same living conditions as the foregoing groups and fed on a mixed diet of oats, alfalfa and greens. At the end of the two year period they were killed. No sclerosis of either type was found in either aorta or coronary arteries. The blood pressure averaged 74 mm., which is normal. The urine did not give evidence of kidney damage. The nonprotein nitrogen and urea nitrogen of the blood remained normal.

COMMENT

The term arteriosclerosis has been employed here because of its general use, although Marchand's term, atherosclerosis, more accurately describes the pathologic condition as worked out by many investigators.

The earliest changes visible at necropsy consist of small raised yellow specks in the intima. These are due to a deposition of fat droplets containing cholesterin esters in the extracellular cement substance of the intima, secondary to a loosening and swelling of this cement substance.[4] The combined changes result in a swelling or thickening of the intima.

These early changes may regress or may progress. In the latter event, the cement substance fuses into a hyaline mass. The surrounding connective tissue is stimulated by this process and these areas become

Fig. 6.—Early change limited to intima of aorta and consisting of swelling of intercellular cement substance and beginning deposition of hyaline material: *A*, intima, and *B*, media.

covered with newly formed connective tissue. This new connective tissue swells and a deposition of hyaline material again occurs. Thus, layer is added to layer. In this area the deposition of fatty substances continues until the tissue cells and intracellular substance become so overloaded with fatty material that necrosis occurs. The cholesterin esters split up. Cholesterin is freed and precipitates out as crystals. The liberated fatty acids form soaps, the calcium soap leading to the incrustation and calcification that characterize the atheromatous ulcer.

Many of our animals presented arteriosclerotic changes, the counterpart of human sclerosis, as described above (figs. 5 to 10). In the aortas of these animals the earliest lesion was found to be primarily the

4. Aschoff, Ludwig: Arteriosclerosis, New York, Paul B. Hoeber, 1924.

swelling of the intercellular cement substance. This was followed by a deposition of fat substances, of hyaline material and finally of calcium soaps. These changes occurred with greatest frequency in those animals on a 20 per cent liver protein diet in which the most marked increase in blood pressure was obtained, whose kidneys gave evidence of a nephritis, and whose blood gave evidence of retained end products of protein metabolism. The urines of these animals were continuously acid.

The factors responsible for the increased blood pressure and the arteriosclerosis may have been excessive protein diet, excess of cholesterol in the diet, or excessively acid urine over a long period of time.

The question as to whether increased blood pressure is responsible for degenerative changes in the kidneys and blood vessels, whether the process is reversed, or whether both these changes are dependent on some

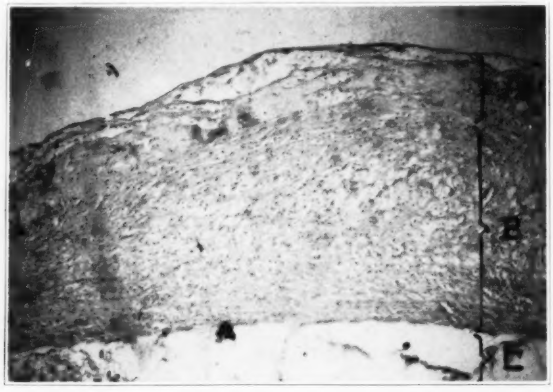

Fig. 7.—More marked intimal change, a further step in the process of sclerosis: *A*, intima; *B*, media, and *C*, adventitia.

primary etiologic factor, is answered in part by our results. The highest experimental blood pressures were obtained in animals that at necropsy presented the most extensive sclerosis of the aorta. It is also true that the highest blood pressures and most extensive blood vessel changes were obtained in the group of animals on the diet that had the most acid urines (the liver group).

Whether the changes were dependent on excessive cholesterin or excessive protein is elucidated by our experiments. The conclusion of German investigators, particularly Schmidtmann,[5] Antischkow,[6]

5. Schmidtmann, M.: Experimentelle Studien zur Pathogenese der Arteriosklerose, Virchows Arch. f. path. Anat. **237**:1, 1922.

6. Antischkow, N.: Ueber die experimentelle Atherosklerose der Aorta beim Meerschweinchen, Beitr. z. path. Anat. u. z. allg. Pathol. **70**:265, 1922.

Mönckeberg,[7] Schoenheimer,[8] Aschoff and others, was that cholesterol is responsible for the arteriosclerosis that occurs in rabbits, guinea-pigs and cats, which are the only experimental animals in which these changes have been produced to date. The diets of these animals have contained considerable amounts of cholesterol or of cholesterol and neutral fats. When the latter are added, the resulting sclerosis seems more pronounced than when the same amount of cholesterol alone is given. In support of this contention, the findings of Kon are cited. He was unable to produce arteriosclerosis in rabbits fed a cholesterin free liver diet. Antischkow sums up the situation by saying, "Without cholesterol, no sclerosis." Newburgh,[3] as far as we can find, is the only investigator to raise an objection to this conclusion. As a result of feeding high protein diets he obtained well defined arteriosclerosis. Since his diets

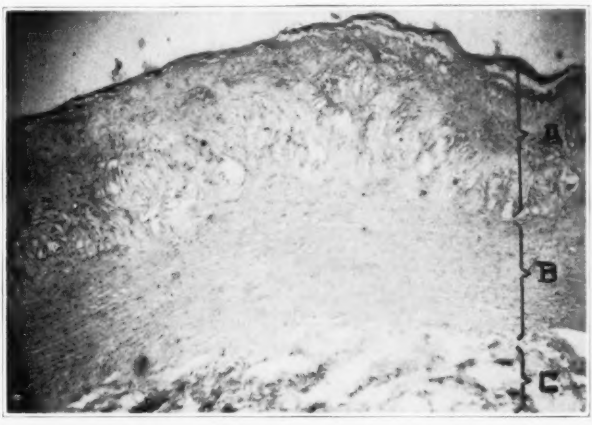

Fig. 8.—Marked thickening of intima, the result of arterial sclerotic degenerative changes: *A*, intima; *B*, media, and *C*, adventitia.

contained considerably smaller amounts of cholesterol than the amounts that are held necessary to produce experimental arteriosclerosis, he believes that the high protein factor is responsible for this degenerative change.

The amount of cholesterol in our liver diet will be made a matter of further study. Our grain diet, however, contained no cholesterol and yet seven of eleven animals developed a well defined and extensive arteriosclerosis. In this instance the increased blood pressure, the diet of high protein or the acid urines resulting from the ingestion of the protein

7. Mönckeberg, J. G.: Arteriosclerose, Klin. Wchnschr. **3**:1473 (Aug. 12) 1924.

8. Schoenheimer, R.: Ueber die experimentelle Cholesterin-Krankheit der Kaninchen, Virchows Arch. f. path. Anat. **1**:249-250, 1924.

diet must have been responsible for the sclerosis. We find that Newburgh's contention is just, that cholesterol is not necessary to the experimental production of arteriosclerosis, and that high protein diets may produce this change.

We attempted to determine whether the factor of disturbed acid-base balance as expressed by the long continued secretion of excessively acid urine might in itself be responsible for the increased blood pressure and the degenerative blood vessel changes. To this end, the high protein (36 per cent) soy bean diet was given. The vegetable protein resulted in the excretion of a urine whose p_H held around 9.0. The carbon dioxide of the blood serum averaged almost twice as high, 59 per cent by volume as against the control animals, 30 per cent by volume. While clinical evidence of kidney damage and an increase in

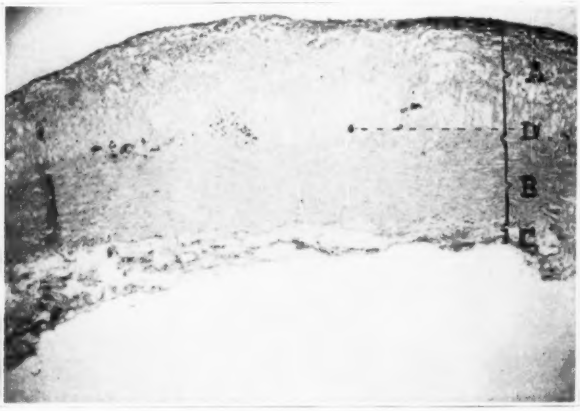

Fig. 9.—Early deposition of calcium in arterial sclerotic area: *A*, intima; *B*, media; *C*, adventitia, and *D*, calcium deposits.

the blood pressure did occur, yet no instance of intimal arteriosclerosis was found in any of the twelve animals of this group. One would expect kidney damage from the long continued alkalosis that resulted from the soy bean diet. Fischer [9] has shown that excessive alkali is capable of producing kidney injury. Henderson, Palmer and Newburgh [10] have drawn the same conclusion. Our experiments show clearly that a long continued disturbance of the acid-base balance of rabbits on the alkaline side is capable of causing a moderate hypertension and of causing kidney damage, but that it does not produce arterio-

9. Fischer, M.: Edema and Nephritis, New York, John Wiley & Sons, 1915.

10. Henderson, L. J.; Palmer, W. W., and Newburgh, L. H.: The Swelling of Colloids and Hydrogen Ion Concentration, J. Pharm. & Exper. Therap. **5**:449, 1914.

sclerosis. The absence of arteriosclerosis may have been due to the fact that the blood pressure was not sufficiently increased in height or long enough maintained to produce this change.

The occurrence of sclerosis of the vessels in the eye grounds was sought for in the animals of the various groups. No changes were noted. The spreading out of the optic nerve over the retina of the rabbit eye makes the detection of blood vessels difficult. A marked arcus senilis occurred in each eye of a female rabbit in the liver group. The occurrence of this condition was noted by Schoenheimer as occurring in female rabbits only, on a high cholesterol diet.

The presence of arteriosclerosis in vessels other than the aorta has been found particularly by German investigators using high cholesterol diets. The arteries of the spleen, kidneys, liver and lungs have been

Fig. 10.—More extensive calcium deposits in an arterial sclerotic plaque of aorta from rabbit on a liver diet for sixteen months: *A*, intima; *B*, media, and *C*, adventitia.

affected. In our groups, changes in these arteries were slight. The coronary arteries, however, were frequently and extensively involved. The swelling here occasionally almost occluded the lumen of these vessels. This occurred most frequently in the left coronary artery. In the same animals the blood pressures were the highest that we obtained and the thickness of the muscle and of the left ventricular wall was greater than in the control group. The arteriosclerosis was frequently seen to involve the small vessels in the myocardium.

The presence of fat was sought for in the myocardium, liver and kidneys of the animals that presented the sclerotic changes. The livers of the liver diet group contained considerable amounts of lipoid material as demonstrated by the fat stain sudan III. The fat was present as fine dustlike particles and as larger droplets in the parenchymal cells of the

periphery of the lobule and in many instances extended well in toward the central vein. There was also easily demonstrable fat in the walls of the smaller arteries of the myocardium and scattered through the muscle cells themselves. In some instances the papillary muscles contained striking amounts of fat.

The stainable lipoid material in the livers, kidneys and myocardium of the grain and soy bean groups of animals was little, if any, greater than in the control group. This might be expected, since the diets of the latter groups contained no cholesterin.

Schoenheimer noted increased amounts of stainable lipoid in the hearts of all animals fed on a cholesterol diet for 100 days or longer. The fat occurred as fine striations and netlike structures involving both the papillary muscles and the walls of the ventricles. He concluded that these changes simulated Tigerung in man. He also noted thickening of the walls of the ventricles in the animals that had a marked arteriosclerosis of the coronary arteries. Our group of animals fed on a liver high protein diet presented changes coinciding with his.

SUMMARY

Four groups of factors have been outlined by numerous investigators as of etiologic importance in the production of arteriosclerosis and increased blood pressure.

To these a fifth group has more recently been added, i. e., a disturbance of the acid-base balance resulting in the excretion of excessively acid urines. This disturbance of balance has been produced by high protein diets both in man and in experimental animals. The dietary of the American people, with its excess of meat, cereals and bread, is of this acid type.

By feeding various excessive protein diets to experimental animals for periods as long as two years, we have obtained increased blood pressures. The animals in which the most marked increase of blood pressures were obtained presented extensive arteriosclerosis of the aorta and in many instances of the coronary arteries. Evidence of kidney damage was also obtained, as demonstrated by chemical studies of the blood and of the urine.

The histology of arteriosclerosis in rabbits is similar to that of human arteriosclerosis.

Spontaneous sclerosis in rabbits has an absolutely different histologic picture.

Our experiments demonstrate that increased blood pressure and arteriosclerosis can be produced without an increase of cholesterol in the diet.

Excessive amounts of fat were found in the liver and myocardium of animals whose diet was high in cholesterol.

DIAGNOSIS OF PULMONARY NEOPLASM*

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NEW YORK

There appears to have been a striking increase in the number of cases of cancer of the lung during recent years in America and Europe. That this increase is not altogether the result of greater precision in diagnosis is evident when we consider that not only clinicians have noted it, but also pathologists have reported to this effect. Douglass Symmers has observed this increase in the pathologic laboratories of the Bellevue Hospital in New York, and Hampeln,[1] Staehelin,[2] Assmann,[3] Berblinger,[4] Holzer,[5] Heilmann,[6] Kikuth,[7] and others in Europe have published statistics to this effect. The problem to be cleared up by those engaged in cancer research is whether this goes hand in hand with the increase in visceral cancer recently observed in civilized countries or there is some special etiologic factor operative in the case of the lungs, such as dust in modern industrial centers, as noted by Hampeln,[1] Heilmann[6] and others, and the influenza epidemic, which left in its trail numerous injured lungs.[8]

In this article we deal with the clinical aspects of sixty cases of primary malignant disease of the bronchi, lung and pleura in Montefiore Hospital during the last ten years. In thirty-six, necropsies were obtained. We found that contrary to the prevailing opinion in clinical circles, the diagnosis of this disease can be made during life in the majority of cases.

---

* From the tuberculosis division of the Montefiore Hospital and the Bedford Hills Sanatorium for Incipient Tuberculosis.

1. Hampeln: Zur Symptomatologie und Diagnose der primären malignen Lungentumoren, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **31**:672, 1919.

2. Staehelin, R.: Zunahme des primären Lungenkrebses, Klin. Wchnschr. **4**:1853, 1925.

3. Assmann, H.: Zur Frage der Pathogenese und zur Klinik des Bronchialkrebses, Med. Klin. **20**:1757; 1796, 1924.

4. Berblinger, W.: Die Zunahme des primären Lungenkrebses, Klin. Wchnschr. **4**:913 (May 7) 1925.

5. Holzer, H.: Zur Frage der Häufigkeit des Bronchialkrebses, Med. Klin. **21**:1235, 1925.

6. Heilmann, P.: Ueber die Zunahme des primären Lungencarcinoms, Virchows Arch. f. path. Anat. **255**:549, 1925.

7. Kikuth, W.: Ueber Lungencarcinom, Virchows Arch. f. path. Anat. **255**: 107, 1925.

8. Moise, T. S.: Carcinoma of the Lung, Arch. Int. Med. **28**:733 (Dec.) 1921. Assmann (Footnote 3). Berblinger (Footnote 4).

The average age of these sixty patients was 55 years. The age period distribution was as follows:

Below 40	8, or 13.33 per cent
From 40 to 50	11, or 18.34 per cent
From 50 to 60	23, or 38.33 per cent
From 60 to 70	14, or 23.33 per cent
70 and over	4, or 6.67 per cent

The majority of cases occurred in persons between 40 and 70 years of age, which is the age distribution of cancer in general. The youngest of our hospital patients was 31, and the oldest 84, but I have seen two cases in persons 18 and 21, respectively. There have been reported even younger persons with malignant disease of the lung.

Of our patients forty-four, or 73.3 per cent, were men and sixteen, or 26.6 per cent, were women. Most other writers have found that men predominate. Among the 374 cases compiled by Adler [9] 71.9 per cent were in men.

NECROPSY FINDINGS

Necropsies were obtained in thirty-six cases and superficial glands were excised for microscopic study in eight. Of these, we found that thirty-five were carcinomas and only one a spindle cell sarcoma. The great predominance of carcinoma of the lung has been noted by nearly all who have reported on large series of cases. Only Rolleston and Trevor [10] state that most pulmonary tumors are sarcomas, but this is contrary to all other observations, and it would seem that Barron [11] is right in assuming some confusion on their part. Though it has been stated that cancer is considerably more frequent in the right lung and theoretical explanations have been advanced for this supposed phenomenon, in our series the left lung was the seat of the tumor in 56.6 per cent of the cases. There was no predominance of either side in the 374 cases compiled by Adler.[9]

The macroscopic picture of the carcinomatous lung is exceedingly varied, owing not only to the variety of forms in which the tumor itself may grow but even more to secondary nutritive and circulatory disturbances in the tumor tissue and the mechanical consequences of compression by the growing tumor; to these may be added changes due to infection of the growth with any of the pyogenic microorganisms, which is not infrequent.

As regards their macroscopic appearance, our cases may be divided into four groups:

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9. Adler, I.: Primary Malignant Growths of the Lungs and Bronchi, New York, 1912.
10. Rolleston and Trevor: Brit. M. J. **1**:361, 1903.
11. Barron, M.: Carcinoma of the Lung, Arch. Surg. **4**:624 (May) 1922.

1. The most common picture is that of an irregularly delimited yellowish or grayish mass in the vicinty of the hilum, infiltrating the parenchyma more peripherally, usually of the hilum of the upper lobe. On section of the tumor one can often discover the still patent lumen of the bronchus from which the tumor took its origin.

2. Another, not nearly so common, finding is that of a coarsely nodular mass embedded in the parenchyma of any part of the lung with much better defined outlines than the tumors of the first mentioned group.

3. A further rare form is a diffuse carcinomatous infiltration of one or more lobes, whose appearance presents great similarity to that of an extensive caseous pneumonia.

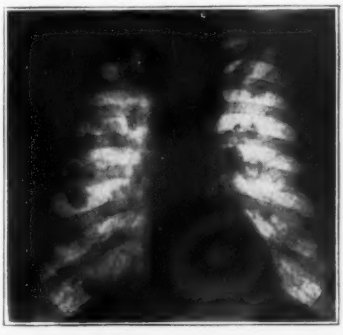

Fig. 1.—Metastatic deposits in lungs from carcinoma of stomach; each deposit is clearly seen.

4. Three of our cases were the much disputed "endothelioma of the pleura," the lung being covered by a thick nodular sheet. The so-called primary miliary carcinosis, though it undoubtedly occurs, was not observed in our series, but we have seen it many times in cases of secondary cancer of the lung (fig. 3). Closely neighboring on the primary growth are often seen metastases to the pulmonary parenchyma. Extensions from the primary growth along the peribronchial and, not so commonly, the perivascular lymphatics may form a prominent feature. In some cases the eye is first struck, when the breast plate is removed, by peculiar patterns outlined on the pleural surface through the permeation of the subpleural lymphatics by carcinoma cells, known as lymphangitis carcinomatosa.

The relations of the growth to the bronchus of origin are of primary interest in explaining the physical signs on which we lay so much stress in the diagnosis of these cases. Rather uncommonly the tumor grows along the bronchial wall forming an eccentric envelopment, thus con-

verting the bronchus into a thick walled tube. But as a rule there is extreme narrowing. This may be due to an annular growth gradually diminishing the lumen, or to complete obturation by a ball-like mass of tumor tissue.

Secondary changes in the tumor itself and reactive phenomena on the part of the adjacent lung tissue form an integral part of the picture. The tumor may proliferate so rapidly as to outgrow its blood supply

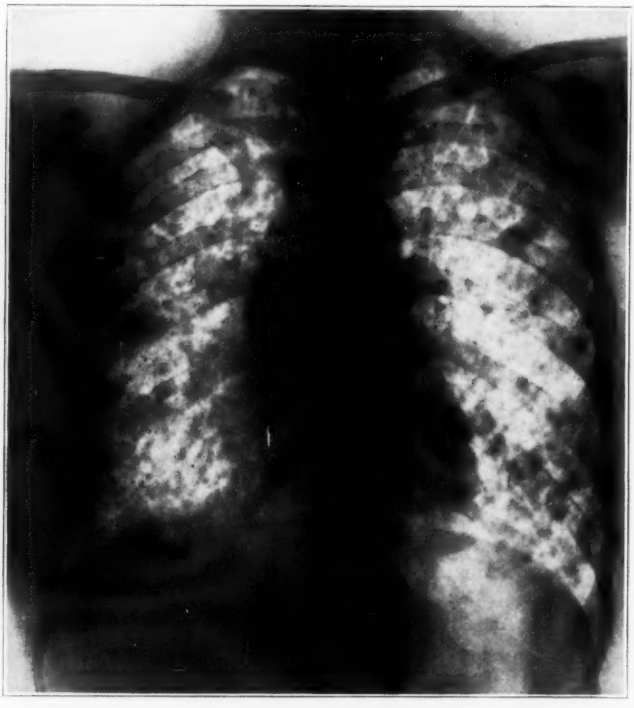

Fig. 2.—Miliary carcinosis, formed by hematogenous dissemination from a carcinoma of the breast.

with consequent necrosis of the central portions. The necrotic tissue may be evacuated through the bronchus with resulting cavity formation. Very much as in tuberculosis, these cavities may become secondarily infected and at necropsy are often found full of pus and lined with a pyogenic membrane. Aneurysmal dilatations of vessels may be found projecting into the cavity. There may be many discrete cavities, or one large one. In two cases there was one large cavity with a thin wall of tumor tissue (figs. 21 and 22) recognizable as such only on microscopic

examination, without any metastases either in the lung or any other organ. In four cases an entire lobe was thus destroyed. While every form of bronchial carcinoma may bleed, thus producing streaky sputum, those with necrosis and cavity formation may be accompanied by copious and even fatal hemorrhages when a large vessel is eroded. Usually there are considerable areas of chronic indurative pneumonia surrounding the neoplasm, but there are cases in which the adjacent lung remains quite normal, as was the case with the large cavities just mentioned (figs. 19 to 21). There may be quite extensive atelectasis in the

Fig. 3

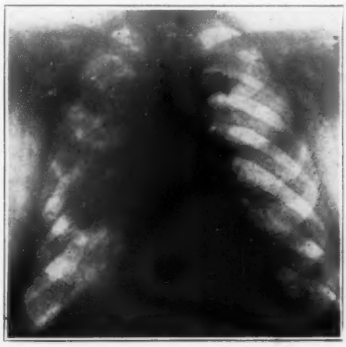

Fig. 4

Fig. 3.—Primary carcinoma of left lung; cloudiness at periphery beyond the limits of the solid tumor, due to atelectasis, and also elevation of diaphragm should be noted.

Fig. 4.—Primary carcinoma of right lung; upper part of tumor broken down.

portions of the lung whose bronchial supply has been impaired or obliterated (figs. 3, 4 and 11). The frequent serous, sanguineous and purulent pleural effusion accompanying lung tumor are discussed later on.

The histology and more the histogenesis of pulmonary carcinoma have been moot questions for years, and as yet complete unanimity has not been attained. The reasons for the great difficulty in interpreting the cytology of these tumors in terms of their histogenesis are evident when one considers that while the epithelium lining the bronchopulmonary system is continuous from the trachea to the alveoli, gradual changes in the morphology of the lining epithelial cells occur in the transition from the ciliated columnar cells of the larger bronchi, through cuboidal forms, to the flat alveolar epithelium. Moreover, the bronchial mucous glands consist merely of modified bronchial epithelium.

Instances of metaplasia of the columnar cells lining the larger bronchi into squamous cells are very common as a result of inflammatory processes. From these considerations it is evident how unsafe it is to draw conclusions as to the histogenesis of the tumor from morphologic obsertions. However, it is generally agreed that pulmonary carcinoma is almost synonymous with bronchial carcinoma; that neoplasms originating from the alveolar epithelium are rare, though they probably occur. A certain group of these tumors unquestionably originates from the bronchial mucous glands, as was long ago demonstrated by Langhans.[12] Certain others seem to originate quite certainly from the ciliated columnar epithelium of the larger bronchi. Bearing in mind the difficulties just enumerated, we will not attempt to classify the tumors of our series

Fig. 5.—Primary carcinoma of the right lung extending along the lymphatics, in lymphangitis carcinomatosa.

histogenetically, contenting ourselves with the mere statement that in twenty of the thirty-six carcinomas, the predominating type of cell was columnar and in most cases showed more or less tendency to the formation of glandlike figures, i. e., adenocarcinoma. In twelve cases the tumor was made up of squamous cells in which cornification with the formation of epithelial pearls, epithelioma, was to be discerned. Three belonged to the group ordinarily termed endothelioma of the pleura.

METASTASES

In nearly all cases of carcinoma of the lung other organs are involved, either by direct extension of the primary growth (mediastinal organs, chest wall) or metastasis. Widespread metastases may occur from small primary growths, but we have seen cases in which the tumor remained

12. Langhans: Primärer Krebs d. Trachea u. Bronchien, Virchows Arch. f. path. Anat. **53**:470, 1871.

in the lung for months to a fatal termination without any metastases at all. One point must be emphasized, and this has a clinical bearing: Clinically discernible metastases almost always occur late in the course of cancer of the lung, though there are striking exceptions, particularly as regards skeletal metastases. In primary sarcoma of the lung, on the contrary, metastases are usually early. Some patients with primary carcinoma of the lung go along for one or two years, in rare instances even longer, with the growth confined to its original seat in the lung. At the necropsy the opposite lung may be found free from neoplastic implantation; this was so in most of our cases. The thirty-six cases in which necropsies were performed showed the following metastases:

Regional lymph nodes	30
Distant lymph nodes	17
Lung	(9 to opposite lung) 12
Liver	10
Suprarenals	8
Kidneys	6
Bones	2
Dura	2
Brain	2
Thyroid	1
Spleen	1
Pancreas	1
Rectum	1

In many cases the problem arises whether the growth discovered clinically in the lung is primary or secondary, i. e., a metastatic deposit from a tumor in some other organ which has escaped detection. Some, in fact, maintain that the vast majority of cancers of the lung are secondary to cancer of the esophagus, thyroid, prostate or suprarenals. In the cases reported here, a careful search was made to find the original site of the neoplasm, and when found in another organ, the case was excluded from this series. We must acknowledge that while we are satisfied that in all our cases the tumor was primary in the bronchi, lung or pleura, it is possible that some were in fact of the secondary type. In this connection it is important to mention that even after a careful necropsy this problem cannot be settled in every case. In several of our cases competent pathologists could not agree whether they should be considered primary or secondary. Of course the clinician is more liable to err in this respect than those who have opportunities to dissect the body.

CLINICAL FEATURES

The difficulties at attempts at diagnosis of primary cancer of the lung will be appreciated when we mention that 80 per cent of our patients were sent in with diagnoses of other diseases even though most were

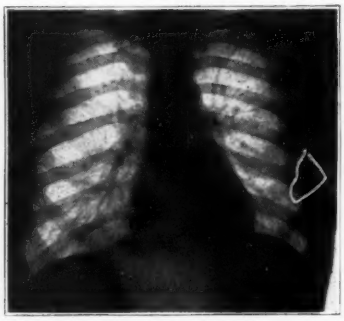

Fig. 6

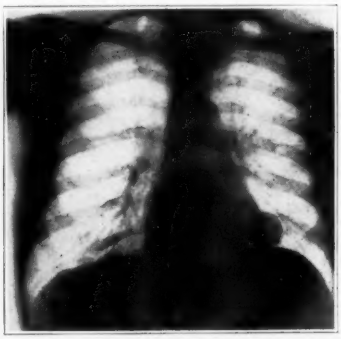

Fig. 7

Fig. 6.—Hypernephroma, April 10, 1923, showing no involvement of lungs; physical examination indicated tumor in left base.

Fig. 7.—Same patient as shown in figure 6, Sept. 4, 1924; small tumor clearly shown near cardiac apex.

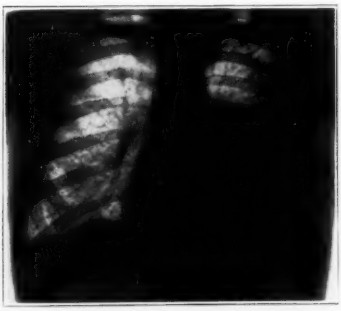

Fig. 8.—Same patient as shown in figures 6 and 7, Nov. 13, 1924; lower half of left lung is replaced by solid tumor mass.

observed in other hospitals before admission to Montefiore. This is not exceptional as can be seen from textbooks on medicine and monographs on diseases of the lungs. In most it is stated that the majority of cases are revealed only on the necropsy table. Sehrt [13] compiled from the literature 210 cases and of these only six were diagnosed during life. Adler's [9] compilation shows similar results. Even with the most modern methods of diagnosis things have not improved to a desirable extent. Kikuth [7] found that at the Eppendorf Hospital in Hamburg only 34 per cent of 246 cases were diagnosed during life; 11 per cent were suspected, and in 55 per cent diagnoses of other diseases were made. Likewise, in the Basel clinic Staehelin [2] found that only in 30 per cent were correct diagnoses made during life; in 11 per cent cancer was suspected; in 3 per cent mediastinal tumor was diagnosed, and in 51 per cent diagnoses of other diseases were made.

It has, however, been our experience that cancer of the lung has a semeiology of its own and that the diagnosis offers no insuperable difficulties. When the symptomatology and physical signs are carefully gone into and properly interpreted the chances of error are no higher than in other chronic pulmonary diseases. While roentgen-ray examination and the study of the cytology of the sputum and pleural exudates are invaluable in many cases and mostly as corroborative evidence, the history, symptomatology and physical signs are most important. Relying mainly on the just mentioned criteria we only rarely miss a case.

SYMPTOMS

The onset is insidious in nearly all cases, though many patients assert that some symptom, commonly cough, dyspnea, pain in the chest, or hemoptysis, has suddenly made its appearance. In four cases that I observed the patients stated that the onset was sudden with chill, fever, pain and cough, simulating pneumonia, for which they were treated. It seems rational that these patients had small neoplastic formations in the bronchi which gave slight or no symptoms, and that the pneumonia was an accidental incident at that time. After recovery from the pneumonia the symptoms of cancer of the lung were more clearly defined. On the other hand the tumor may have been causally related with the origin of the pneumonia. Two patients maintained that the onset followed injury to the chest, and though several authors have mentioned traumatic cancer of the lung it would seem more rational to consider the injuries as mere coincidences. One patient stated that the first symptom he noted was hoarseness, but he had definite symptoms referable to the chest for months to which he paid no attention. Some patients had

13. Sehrt: Beitrag. zur Kenntnis des primären Lungencarcinoms, Inaugural Dissertation, Leipzig, 1904.

been suffering from chronic pulmonary or bronchial diseases, especially bronchitis, emphysema, bronchiectasis and even tuberculosis, and here the onset of the new disease was not marked by any striking changes in the symptomatology.

In over 90 per cent of the cases cough appears to have been the first symptom. At first dry and hacking, it later on becomes productive of sputum which, as a rule, shows no characteristic traits. It is clear that when the tumor is of the parenchymatous type, or grows from the root of the lung into the parenchyma, the cough may be unproductive for a comparatively long time. In the cases in which the neoplasm grows within the lumen of, or plugs, a bronchus, or presses against the lower end of the trachea, especially at its bifurcation, the cough is paroxysmal, at times agonizing or emetic. In the later stages, when gangrene of the tumor is not uncommon, the amount of sputum may be enormous, at times malodorous.

Only exceptionally may the diagnosis be made from a study of the cytology of the sputum. In far advanced cases clumps of tumor tissue are expectorated at times and a microscopic examination of these clumps may help in the identification of the variety of neoplasm. We must emphasize, however, that individual cells are of little, if any, help in diagnosis because epithelial cells derived from the mucous lining of the respiratory tract appear in many catarrhal conditions as well as in tuberculosis. In some instances, as was first described by Lenhartz,[14] great numbers of large, spherical cells, loaded with fat granules are found and he considered them pathognomonic of cancer of the lung. But they may also be found in other respiratory diseases, as Lenhartz himself acknowledged. At all events, the cytology of the sputum has been of assistance to us in early diagnosis in exceedingly few instances only and then has been merely corroborative.

Bloody sputum may occur early in the disease, but this is exceptional. Later on it is quite common and 60 per cent of our patients had hemoptysis during the course of the disease. When the tumor begins to decay, the sputum is mixed with blood, and may present the appearance of raspberry juice or currant jelly, of which some writers have spoken. When superinfection occurs, or disintegration due to circulatory changes in the tumor mass takes place, copious, uncontrollable and at times fatal hemorrhages may result. Four of our patients succumbed to pulmonary hemorrhage.

Dyspnea is another early symptom. In fifty-six out of our sixty cases it was one of the earliest symptoms that urged the patient to seek medical advice. It is quite mild in the beginning but becomes severe and, in many cases, hard to bear, not even being relieved by rest in bed. In

14. Lenhartz, in Ebstein: Handbuch. d. prakt. Med., Ed. 2, 1905, **4**.

persons of the cancer age dyspnea, to which cannot be attributed a cardiac origin secondary to a valvular lesion, hypertension or pulmonary emphysema, when combined with cough, pain in the chest and slight hemoptysis, should excite suspicion. Dyspnea is exceedingly rare in early chronic phthisis and remains rare as long as the lesion is not extensive and there is no complicating pleural effusion or a pneumothorax, miliary involvement of the lungs, toxic myocardial injury or cardiac displacement in cirrhotic phthisis. In cancer of the lung the dyspnea is to some degree due to infiltration of the peribronchial and perivascular lymph vessels by neoplastic cells, lymphangitis carcinomatosa, causing rigidity of the lung and compression of the alveoli. This very type of dyspnea is also seen in miliary carcinomatosis, which is almost always secondary. When the tumor is larger, the dyspnea is aggravated by plugging of a large bronchus, rarely even of the trachea, the growth extending within the tube or compressing it from without. In several cases the dyspnea, bearable at first, suddenly became aggravated and proved fatal within a short time, indicating extension of the tumor in such a manner as to compress the trachea. In a case of this sort we found at the necropsy that the tumor in the left lung extended to the pleura, mediastinum and, through the pericardium, into the left auricle. In two others the tumor extended into the right ventricle, causing intense dyspnea and cyanosis of the entire body. Another curious phenomenon has been observed: The intensity of the dyspnea was more or less intermittent in many cases, indicating that the tumor which exerted pressure on a bronchus moved away to some degree because of mechanical factors. In one case in which pneumothorax was induced for diagnostic purposes the growth was at first seen on the roentgenogram clearly, but later on the shadow indicating the tumor disappeared behind the shadow of the mediastinum and made us suspect an incorrect diagnosis. At the necropsy, however, the growth was found.

Stridor is another symptom that some writers consider characteristic, but it was only rarely observed among our patients. It occurs mainly when the mediastinal glands are implicated by extension of the growth or by metastases compressing the trachea. It was encountered in only four of our cases and only shortly before the end. Pleural effusion, which, as we shall see later on, occurs in 50 per cent of cases, aggravates the dyspnea.

Cyanosis is seen early in about 50 per cent of cases. Various degrees may be observed, but it is most severe when the tumor grows in the direction of the superior vena cava compressing this vessel. Acrocyanosis, as well as clubbed fingers, have been observed in 25 per cent of cases. Clubbed fingers appearing in a patient of middle age should urge careful examination of the lungs for tumor.

In some cases, though few, the course of the disease is afebrile throughout. In the majority careful thermometry reveals a mild subfebrile temperature, not unlike that seen in tuberculosis. Superinfection with pyogenic micro-organisms produces pronounced fever, at times as high as 104 F., and when in addition there is pain in the chest and fetid sputum a diagnosis of abscess or gangrene of the lung is made. This was the diagnosis in five cases admitted to our service, and in one the abscess was actually operated on. Any type of fever may occur, continuous, remittent, intermittent and hectic. Profuse sweating is not uncommon and many patients complain of night sweats.

It is noteworthy that emaciation is not an early symptom of cancer of the lung, a fact already observed by Laënnec.[15] Most of our patients

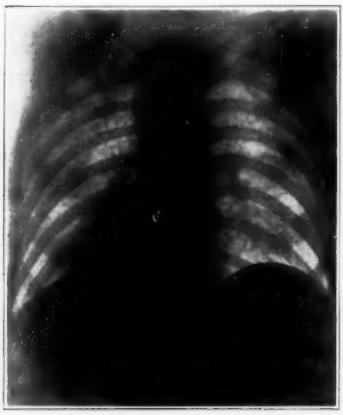

Fig. 9

Fig. 10

Fig. 9.—Practically normal appearance of patient, March 18, 1924, although physical examination showed probable tumor in lower lobe of left lung.

Fig. 10.—Same patient as shown in figure 9, May 30, 1924; tumor is clearly seen.

retained their weight for months; those treated for tuberculosis and urged to rest and eat excessively even gained in weight for some time. We have seen as much as 20 pounds (9 Kg.) gained by patients within three or four months. In senile patients with otherwise latent cancer of the lung, the only striking symptom may be extreme emaciation, "senile marasmus."

Pain in the chest is one of the cardinal symptoms of *primary* cancer of the lung. In fact, it was complained of by more than 90 per cent of our patients at an early period of the disease. It may be localized in

15. Laënnec: Traité de l'auscultation médiate, Ed. de la fac. de méd., Paris, 1878, p. 510.

the region over the tumor, or radiate from the chest to the shoulder, or even to the finger tips. When it occurs in the left side and is due to pressure of metastatic deposits on the brachial plexus, it may, together with the dyspnea, simulate stenocardia; hence, such patients are at times treated for "heart disease." The pain may be continuous, but more often it is paroxysmal, simulating so-called intercostal neuralgia for which it is often mistaken. Cutaneous hyperesthesia is common. In several cases under our observation the first symptom that brought the patient to the physician was pain over a localized area of the lumbar spine. We have not been convinced that this was invariably due to early metastasis into the lumbar vertebrae, as is often the case with mammary, prostatic or other varieties of carcinoma with a tendency to bone

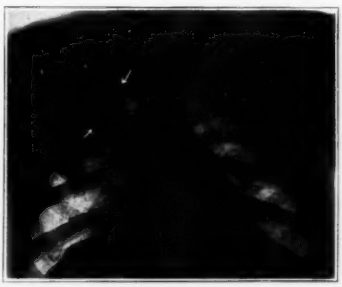

Fig. 11

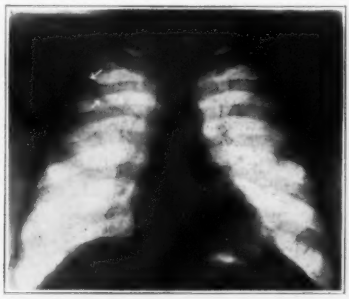

Fig. 12

Fig. 11.—Dec. 7, 1922, solid mass in upper part of right lung, near the periphery, diagnosed tumor.

Fig. 12.—Same patient as shown in figure 11, June 10, 1924; mass has disappeared, leaving sharply delineated shadow extending from hilum to periphery, indicating thickened interlobar fissure.

metastasis. In fact, metastasis is a rather late phenomenon in primary carcinoma of the lung, as has already been stated. In some cases the radiation of the pain was toward the abdomen. One point must be emphasized: Pain is exceptional in secondary carcinoma of the lung, and when it occurs it points to primary neoplasm of the bronchi, lung or pleura.

The distant pressure symptoms, spoken of so much in textbooks, are only exceptionally observed in pulmonary neoplasms, though they are quite common in mediastinal growths. Inequality of the pupils was observed only in three cases of this series. Likewise dilatation of the superficial veins of the chest and arm is only rarely seen, while it occurs frequently in mediastinal tumors which, exerting pressure on the superior vena cava, produce dilatation and at times thrombosis of the superficial veins of the chest, arm, neck and even the face. The jugular

vein may be seen dilated and pulsating strongly in rare instances. Pronounced, even ghastly cyanosis of the neck, face and arm also goes with mediastinal growths. When the collateral venous circulation is insufficient to overcome the obstruction, in addition to cyanosis edema of the neck, face and arm also results. When the innominate vein alone is compressed the cyanosis is unilateral. However, in purely bronchial or parenchymatous neoplasms these symptoms are rare. We have observed them only twice in our series to any notable degree.

Likewise, enlargement of the superficial glands is but rarely met with in the early stages of primary neoplasm of the lung, contrary to Hodgkin's disease and lymphosarcoma. In the terminal stages, the glands in the supraclavicular region and, at times, in the axilla may be felt as enlarged and hard masses. Now and then, we meet with cases in which enlarged and palpable glands can be made out, especially those between the heads of the sternomastoid. It requires careful palpation to feel these glands as small, hard nodules freely movable. In a case of sarcoma of the lung a large mass was seen above the clavicle when the patient exhaled strongly which disappeared down into the thorax during inspiration. In rare instances we noted the glands on the neck enlarged to a degree to be visible on inspection. But it must be emphasized that primary carcinoma only rarely manifests itself thus. Enlarged cervical glands are much more common in lymphosarcoma and malignant granuloma.

DIAGNOSIS

The diagnosis can be made in the vast majority of cases quite early and the site of the growth localized if we bear in mind that clinically the disease manifests itself in three forms:

1. The pulmonary form, simulating tuberculosis.
2. The pleural form, simulating pleurisy, dry or with serous, sanguineous or purulent effusions.
3. The excavating form, simulating abscess and gangrene of the lung.

THE PULMONARY FORM

The insidious appearance of cough, streaky sputum, mild fever, hemoptysis, dyspnea and pain in the chest in a person over 35 years of age should suggest not only tuberculosis or cardiovascular disease but also the likelihood of neoplasm of the lung. At this period of life tuberculosis is most often an exacerbation of an old dormant lesion and there is consequently a history of previous attacks of cough, expectoration and fever. The physical signs indicate a bilaterally active lesion or an active lesion in one lung and a sclerotic lesion in its mate. In tuberculosis there is almost invariably tachycardia, in tumor it is exceptional. Dyspnea is very common in tumor and rare in early tuberculosis. Unless

there are actual signs of pleurisy, acute and annoying pain in the chest is not as a rule a clinical manifestation of early tuberculosis. Pain due to vascular or cardiac disease can usually be accounted for by signs of disease of the heart or aorta which are lacking in cancer of the lung.

PHYSICAL SIGNS

In our experience, physical exploration of the chest is more likely to indicate the location of the growth at an early stage than the roentgen rays. We have repeatedly localized tumors of the lung by percussion and auscultation when the roentgenograms were entirely negative or inconclusive. Figures 6 to 10 show two cases in which the diagnosis was thus made by auscultation and percussion weeks before the roentgen rays revealed the growths unequivocally on the films.

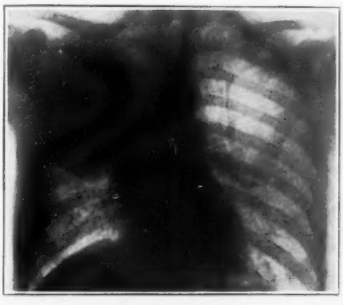

Fig. 13.—Solid mass replacing upper half of right lung simulating tumor; clinical observation and bacteriologic findings, as well as miliary stipplings in right lower lobe indicated pulmonary tuberculosis.

The majority of primary tumors are bronchial and when quite small and growing within or near a bronchus often obliterate or compress the lumen of the tube, either by plugging it or compressing it from without. Atelectasis occurs in the area of lung tissue supplied by the plugged bronchus. The result is that usually we find a limited area of the chest wall which emits a *flat* note on percussion, and the pleximeter finger feels a sense of resistance characteristic of flatness, as when a muscular limb or collection of fluid is percussed. In the majority of cases the bronchus supplying the upper lobe is thus affected, and flatness is elicited just below the clavicle near the sternum, or over the inner part of the supraclavicular fossa. Anteriorly the flat note extends under the sternum beyond the middle line.

Bearing in mind that a flat note is hardly ever elicited over a parenchymatous tuberculous lesion of an apex, and that the dulness never extends beyond the margin of the sternum, the significance of this sign becomes apparent. In tuberculosis the note is dull; at times even a

tympanitic overtone is elicited, but never in tumor. In tumors of the lower lobes of the lung, which are less common than those in the upper lobes, obturation of the supplying bronchus produces somewhat similar signs. A flat note is elicited which may indicate tumor, thick pleura or a pleural effusion. In cases of inflammatory effusions a history of an acute onset with pain and fever will point to a diagnosis. When we deal with a thick pleura there is a long history of tuberculous disease, signs of a concomitant apical lesion, or a history of pneumonia, pleurisy or influenza with pleural effusion months or years prior to the onset of the present illness. In left sided tuberculous lesions, because of pulmonary retraction, the heart is exposed, brought near the chest wall and may be seen pulsating in an abnormal place toward the axilla. This

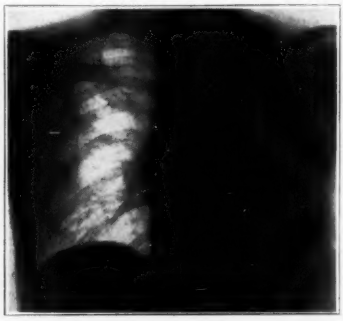

Fig. 14.—Secondary carcinoma of left lung with pleural effusion; necropsy also revealed an active tuberculous lesion in right apex.

is never seen in cases in which the impaired resonance is due to tumor, even though the mediastinum may be displaced toward the affected side. However, in tumors the flat note is in many cases elicited only over one aspect of the chest, while the other remains resonant. Flatness elicited only over part of the anterior aspect of the chest while the posterior remains resonant, or the reverse, is suggestive of tumor, provided of course an encapsulated effusion is excluded.

On auscultation we find feeble, at times completely absent breath sounds and no adventitious sounds over the limited area which was found flat on percussion. In tuberculosis of the upper lobe, even in cases in which caseation or fibrosis are extensive and produce a solid mass, as in figure 13, the note elicited on percussion is either impaired or dull but not flat, and changes in the character of the breath sounds are almost invariably heard, while any of the multifarious adventitious sounds characteristic of infiltration, consolidation, softening or excavation of lung tissue are audible. It may be said that flatness over a limited area, combined with feeble or absent breath sounds, suggests

tumor when found in a person of the cancer age giving a history of an insidious appearance of cough, dyspnea, hemoptysis and pain in the chest.

Tuberculosis with extensive involvement of the lung to such a degree as to produce similar signs is commonly bilateral; signs of a lesion in

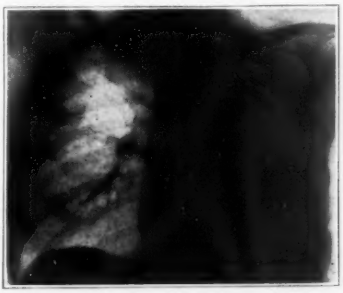

Fig. 15.—Primary carcinoma of left lung with multilocular effusion, some pouches containing serous, others purulent, and still other sanguineous fluid; a surgical operation had been performed.

Fig. 16.—Interlobar effusion secondary to malignant tumor in right lung; subsequently the tumor invaded the entire right side of the chest.

the opposite lung can almost invariably be made out. It is characteristic of primary pulmonary neoplasms that the tumor remains for a long time in one lung while the other continues free from demonstrable pathologic changes. This point is even more emphatically determined by a good roentgenogram. Our illustrations clearly show that the lesions are nearly all unilateral and when these are compared with roentgenograms of advanced tuberculosis the contrast is striking.

In cases in which the tumor advances along the peribronchial lymphatics it may act as a conductor of the sounds in the air tubes and the result is that on auscultation we hear tubular or even amphoric sounds. This sound has been called cornage by Behier.[16] It is usually heard near the sternum or in the interscapular space, while similar breath sounds in cases of tuberculous excavations are heard most commonly in the mammillary region, now and then as far out as the axilla

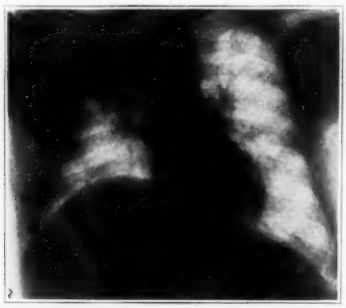

Fig. 17.—Primary tumor of right lung in patient who had symptoms of gangrene.

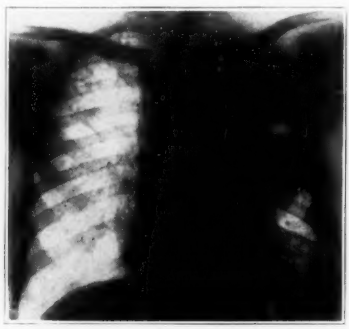

Fig. 18.—Round cell sarcoma primary in the mediastinum, invading the lung; the sputum was positive for tubercle bacilli. At necropsy chronic ulcerative tuberculosis was found in addition to the sarcoma.

above the third rib anteriorly and over the supraspinous fossa posteriorly; the percussion note is dull or even tympanitic, while in tumor it is flat.

It was stated above that the cytologic study of the sputum has been only exceptionally of diagnostic value. Of course, it is important that, despite the extent of the lesion, no tubercle bacilli are discovered. But

16. Behier: Hôpitaux de la Pétrie, Gaz. d. Hôp. **45**:177, 1867.

we have had four cases in which tubercle bacilli were found in the sputum and the necropsy confirmed the diagnosis of the coexistence of cancer and tuberculosis of the lung. Indeed, in cases in which the symptoms and signs enumerated above are clear cut, the discovery of tubercle bacilli in the sputum does not deter us from making a diagnosis of neoplasm of the lung.

ROENTGEN-RAY FINDINGS

Roentgenography, of course, is of decisive diagnostic import in many cases, but often the pictures are misleading, especially in the early stage of the disease. It is now quite widely recognized that the roentgen rays fail in many cases to clear up the diagnosis. Barjon [17] insists that cooperation between the roentgenologist and the clinician is imperative "for there is no pathognomonic roentgen-ray picture of cancer of the pleura and lung." Assmann [3] and Staehelin [2] speak to the same effect. Bryan [18] reports frankly that in nine cases the roentgen-ray diagnosis was unresolved pneumonia in one, tuberculosis in one, abscess in one, and malignancy in six. In our series the diagnosis was repeatedly made clinically while roentgenologists insisted either that the chest was negative, or that the lesion discovered on the plate was tuberculous. Figures 6 to 10 show such cases. A small tumor the size of a cherry, when growing in the center of the pulmonic field, may be seen clearly in the roentgenogram. We see such tumors frequently in secondary growths (fig. 1). But primary tumors, as a rule, grow within or near a large bronchus at the root of the lung. The result is that the shadows produced by them merge with those of the other normal and pathologic hilum structures. Infiltrating tumors produce atelectasis in the parenchyma owing to bronchial stenosis. The density seen on the plate may simulate any other subacute or chronic lesion of the lung. In our experience, several cases of metastatic tumors of the lung were revealed by physical signs long before they could be discerned on the roentgenogram. When the tumor reaches larger dimensions it is only rarely shown on the film as a homogeneous, sharply delimited shadow, such as is pathognomonic of mediastinal growths, particularly lymphosarcoma. The lung tumor, growing from a bronchus and infiltrating the lung along the perivascular and peribronchial lymphatics, spreads out from the hilum, producing a shadow not unlike that seen in certain forms of tuberculosis or pneumokoniosis. In many cases, owing to atelectasis

17. Barjon: Etude clinique et radiologique du cancer mediastino-pleuro-pulmonaire, J. de radiol. et d'électrol. **5**:241 (June) 1921.

18. Bryan, Lloyd: Roentgenological Study of Primary Lung Carcinoma, J. Radiol. **2**:1 (Nov.) 1921.

resulting from obturation of a large bronchus, the lung tissue beyond the actual tumor appears cloudy on the roentgenogram (figs. 3, 4 and 11). In others, in which the neoplasm spreads along the lymphatics, we may see small nodules, like beads, ahead of the main mass, at times following the path of the bronchi, lymphangitis carcinomatosa (fig. 5). On the other hand, we have had several cases in which the entire upper lobe was obscured by the tumor producing a homogeneous shadow, with a sharp line of demarcation suggestive of interlobar effusion (figs. 14 and 23).

It has been said, though it is not as frequently true as some roentgenologists would lead us to believe, that in tuberculosis a good roentgenogram often shows more extensive changes in the lungs than physical signs would indicate. I would add parenthetically that it depends considerably on who makes the physical examination. The reverse is true of most cases of pulmonary neoplasm. Here, because of plugging or compression of a primary bronchus, physical examination often shows an entire lobe flat on percussion and either feeble or entire absence of breath sounds; this leads to the conclusion that the tumor mass has replaced a large area of the parenchyma or a complete lobe. But the roentgenogram may show only a small or moderate sized tumor at the hilum, while the rest of the lung field is either cloudy, because of atelectasis, or entirely normal.

In rare instances the tumor mass, originating at the hilum, extends across the thorax, while above and below this mass the lung field appears normal. Here we have the suspended shadow that may be seen on the fluoroscopic screen moving with respiration. This picture is not unlike that seen in certain cases of interlobar effusion. Two of the latter sort of cases, diagnosed as tumor, surprised us a few months later when we found that the "neoplasm" had disappeared. The fluid was absorbed (figs. 11 and 12). Homogeneous shadows across the chest while the rest of the pulmonic field appears normal may prove baffling to both clinician and roentgenologist. They may indicate tumor or mediastinal or interlobar effusions. In some cases only careful observation for a long period of time will lead to a decisive opinion.

In some cases we have induced a diagnostic pneumothorax for the purpose of clearing up obscure cases.[19] A roentgenogram taken after air is allowed to flow into the pleural cavity collapsing the lung shows the tumor clearly defined (figs. 25 and 26). But this can only be done when there are no adhesions preventing the entry of air into the pleura, and pleural adhesions are rather common.

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19. Fishberg, Maurice: Discernment of Intrathoracic Neoplasms by Aid of Diagnostic Pneumothorax, J. A. M. A. **76**:581 (Feb. 26) 1921.

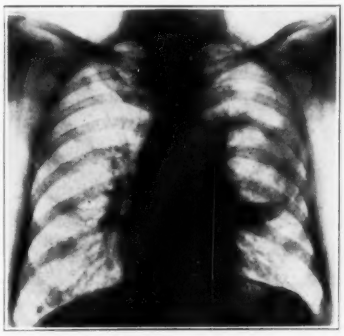

Fig. 19

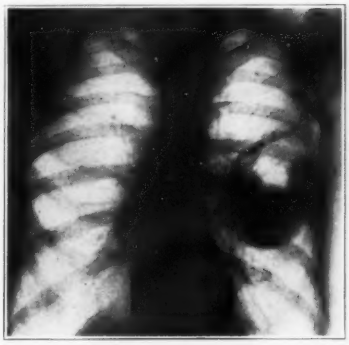

Fig. 20

Fig. 19.—Primary carcinoma of left lung with gangrene making a large abscess cavity.

Fig. 20.—Similar carcinoma to one shown in figure 19.

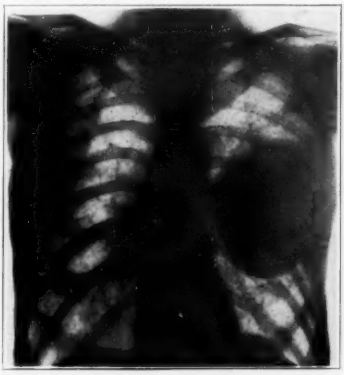

Fig. 21

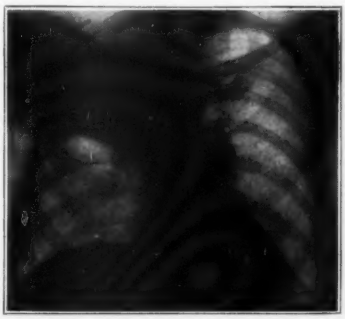

Fig. 22

Fig. 21.—Same patient as in figure 20, who had been given a large dose of opiate in the evening; during the night the secretions in the abscess cavity accumulated, filling it.

Fig. 22.—Primary carcinoma of right lung, showing abscess replacing tumor; secretions withdrawn through an exploratory needle showed neoplastic cells; injection of methylene blue colored the sputum immediately.

THE PLEURAL FORM

A clinical fact, not sufficiently appreciated, is that more than 50 per cent of tumors of the lung are complicated by pleural effusions. Tumors of the lower lobes are more likely to be thus complicated than those of the upper lobes. In thirty-one of our sixty cases, effusions were observed. In sixteen the effusions were serous, in nine sanguineous, and in six purulent. Tumors of the lower lobe come on more insidiously; hence, some patients present themselves for the first time with the pleura filled with fluid. Error in diagnosis is more common than in neoplasm without pleural effusion. The fluid in the pleura is considered sufficient to account for the symptoms and a diagnosis of pleurisy or empyema is made, coupled with a favorable prognosis.

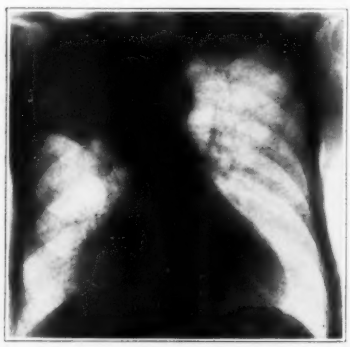

Fig. 23

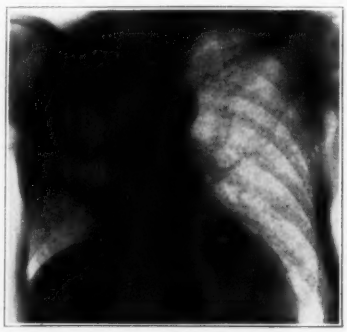

Fig. 24

Fig. 23.—Similar carcinoma to one shown in figure 22, Nov. 6, 1923.

Fig. 24.—Same patient as in figure 23, Dec. 20, 1923; rapid extension of the tumor, now involving the greater part of the right lung, should be noted.

We have found that there are certain clinical features of cancerous effusions which render the diagnosis often quite certain. In three cases operated on for "empyema," surgeons insisted that cancer could be excluded, but necropsies confirmed our conviction that neoplasm of the lung was the primary process.

The age incidence is of importance: Pleurisy complicating tumors of the bronchi and lung occurs mainly in persons over 35 years of age; the vast majority are over 45. Unlike tuberculous and metapneumonic pleurisies, the onset is invariably insidious. The patient gives a history of cough, dyspnea, pain in the chest and perhaps hemoptysis for several weeks or months. But these were only slight annoyances and did not urge the patient to seek medical advice. If a physician was consulted, tuberculous pleurisy or intercostal neuralgia was diagnosed.

The physical signs of malignant pleurisy are almost pathognomonic. In the vast majority of cases physical exploration of the chest, when the findings are properly interpreted, will differentiate cancerous effusions from those due to other causes.

Tuberculous and metapneumonic effusions are characterized, as is well known, by flatness over the area containing fluid, while immediately above the flat area anteriorly there is a zone of tympany, the so-called skodaic resonance. It is this tympanitic zone that is absent above effusions complicating cancer of the lung. Here, a flat note is elicited not only over the effusion but also much further up the chest wall, in most cases as far up as the clavicle.

It is uncommon that the fluid should fill the entire chest in tuberculous, metapneumonic or rheumatic pleurisy. The causes of the flatness all over the affected hemithorax in cancerous effusions are infiltration of the pulmonary tissue by the neoplasm and atelectasis due to obturation of the supplying bronchus, the flatness due to these causes merging with that of the fluid below. It is noteworthy that displacement of the mediastinum to the opposite side, common in tuberculous and metapneumonic effusions, is exceptional in the cancerous varieties; more commonly the mediastinum is drawn to the affected side, owing to extensive atelectasis.

In pleurisies of tuberculous or metapneumonic origin, breath sounds are audible over the lung above the effusion. In many we hear the changed breath sounds indicating a tuberculous process in the upper lobe of the lung; any variety of râles may be audible, depending on the tuberculous changes in the upper lobe of the lung. These are lacking in cancerous effusions. Furthermore, in advanced tuberculosis complicated by pleural effusion auscultatory signs of a lesion in the opposite lung are almost invariably heard, while in primary cancer the opposite lung remains unaffected for a long time or permanently. Obviously, this point is even better appreciated in a roentgenogram.

Pain in the chest is usually the first symptom complained of by patients affected with pleurisy. With the appearance of the effusion, the pain is either ameliorated or disappears altogether. Dyspnea in a patient with a pleural effusion is not as a rule urgent; orthopnea is uncommon. Tapping will relieve both the pain and the dyspnea in patients with pleural effusions of inflammatory origin. Not so with cancerous pleurisy. The pain remains, and may be severe and lancinating, requiring large doses of morphin for its relief. After tapping dyspnea and orthopnea will remain almost as urgent as they were before a large quantity of fluid was withdrawn from the pleural cavity.

Most roentgenologists agree that the fluid in the pleura covers up the neoplastic growth and that all that can be said when viewing a roentgenogram of such a chest is that there is an effusion. Several

years ago, we [19] introduced the following procedure to clear up this sort of case: The fluid is aspirated as completely as possible and air is then introduced into the pleural cavity, using a pneumothorax apparatus for the purpose. A roentgenogram is then made and the tumor may be seen distinctly (figs. 25 to 27). This cannot be done effectively in every case because of pleural adhesions, which are almost as common in cancer of the lung as in tuberculosis.

Cancerous effusions may show rather curious shapes in the roentgenogram. In figure 16 an interlobar effusion is shown as a wedge-shaped, homogeneous shadow, extending horizontally across the chest.

Fig. 25

Fig. 26

Fig. 25.—Pleural effusion secondary to primary carcinoma of lung.

Fig. 26.—Same patient as in figure 25, with diagnostic pneumothorax induced; while complete collapse of the lung could not be obtained because of pleural adhesions, the tumor is seen clearly.

The symptoms and physical signs were those characteristic of neoplasm of the lung. Four months later the tumor had grown to such an extent as to invade three-fourths of the affected hemithorax, and the effusion filled the right pleural cavity.

Exploratory puncture has been carried out in all cases and, unlike our experience with sputum, has often yielded valuable information. It was mentioned above that in the majority of cases the effusion was serous; in sixteen of thirty-one cases the effusion was of this nature. In nine, or 29 per cent, the fluid was sanguineous, while in six, or 19.4 per cent, it was purulent. Attention should be drawn to the high proportion of purulent effusions in cancer of the lung, because we have not met with the statement that empyema is a frequent concomitant of cancer of the lung, though many individual case reports show that pus was found during life or at the necropsy. In one case (fig. 15), a serous

effusion was found at the first exploratory puncture, while at subsequent punctures a little distance away from that point, thick, viscid pus was brought out. It was evident that the effusion was multilocular, some pouches containing serum, others pus, and still others serosanguineous fluid. We have met with three such cases.

A careful search has been made to find cancer cells in fluids removed by thoracocentesis. In all cases the examination was carried out by Dr. David P. Secof,[20] who has had much experience along these lines. The specimen was centrifugated, the sediment fixed in Orth's solution, embedded, cut, and stained with hematoxylin and eosin. Following this technic, Secof reported the presence of cancer cells in about 70 per cent.

Fig. 27

Fig. 28

Fig. 27.—Carcinoma of right lung secondary to cancer of stomach; pleural effusion.

Fig. 28.—Same patient as in figure 27, showing fluid withdrawn from pleura and air let in; tumor is clearly seen.

of fluids from our patients with neoplasm. But it must be mentioned that occasionally even a trained pathologist reports the finding of cancer cells in cases later proved not to be neoplastic. Several such mistakes have occurred in our institution and they constitute a grave limitation of the method. Nevertheless, the microscopic examination of pleural effusions is often a valuable aid in the diagnosis of carcinoma of the lung, and may be the only finding pointing to the existence of such a condition.

The study of the bacterial flora of purulent effusions, while interesting in the individual case, has not yet given us any diagnostic criteria. Various types of pathogenic micro-organisms have been found in the pus taken from patients with cancerous pleurisy.

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20. Secof, D. P.: The Value of Examining Body Fluids for Tumor Cells, Proc. New York Path. Soc. **24,** 1924.

EXCAVATING FORM

A considerable proportion of cases present symptoms not unlike those characteristic of abscess or gangrene of the lung; among the sixty cases in this series, eleven were of this class.

The onset was insidious in eight cases, acute in three. The patient coughs mildly for several weeks and expectorates small amounts of sputum, which may be streaky. Later on he may be more or less dyspneic. Sooner or later the sputum becomes more abundant and assumes a fetid odor. The malodorous character of the sputum may be of various degrees. The pungent stench of pulmonary gangrene in its worst aspects is encountered, while in others it is merely disagreeable, suggestive of chronic pulmonary abscess. Hemoptysis is common and may be only slight, but more commonly the bleeding is copious and threatening. I have seen four cases of fatal hemorrhage due to this cause. The fever is slight in some, but in others it is high, running up to 104 F. and being continuous, while later on it becomes intermittent, at times suggestive of sepsis or progressive pulmonary tuberculosis. Profuse sweating is not uncommon and some complain of exhausting night sweats. As was already mentioned, some of the patients give a history of an acute onset with high fever, pain in the chest and hemoptysis, and a diagnosis of pneumonia is made. The "pneumonia," however, fails to terminate by crisis and because of the continuation of the fever, cough and fetid sputum, a diagnosis of metapneumonic abscess or empyema is made.

The diagnosis of this class of cases is obviously difficult, presenting as they do clear cut stigmas of well known diseases. In pulmonary abscess we often find a known etiologic factor—tonsillectomy, some surgical operation on the upper respiratory tract or mouth, extraction of teeth, aspiration of a foreign body or submersion. The symptoms, fever, cough, pain and expectoration of fetid sputum, make their appearance in from seven to fourteen days after the surgical insult. In metapneumonic abscesses we have a history of pneumonia, which began with a chill, fever, cough and rusty sputum. In cancerous disease of this type, the cough and expectoration have, as a rule, been annoying several weeks or months, when suddenly fever makes its appearance and the sputum becomes fetid. In fact, in our inquiries in cases that began with so-called pneumonia, with but one exception, we elicited the information that the cough, dyspnea, pain and hemoptysis preceded the fever and fetid sputum by several weeks.

The physical signs also point to greater condensation of lung tissue than is found in nonmalignant lung abscesses. Pulmonary abscess cannot as a rule be localized by a physical exploration of the chest. Moreover, flatness over the lesion is exceptional. Over large abscesses tympany is more often elicited on percussion. In abscesses due to

neoplasm, the entire upper lobe is flat, as was already described when discussing the first group of cases. In growths of the lower lobe, the flatness is elicited, as a rule, over only one aspect of the chest, the anterior or the posterior, while the resonance over the other aspect is either normal or but slightly impaired. This is a point that will bear emphasis: if we find flatness anteriorly while posteriorly the resonance is normal, or the reverse, a tumor is to be suspected. Adventitious sounds, such as large and medium sized moist or bubbling râles, when found, are usually of the same character in cancerous abscess as in abscesses of other origin. But in most cases none are perceived. The diagnosis of these cases thus rests merely on the history of an insidious onset and flatness on percussion, coupled with the age period at which cancer usually occurs. Now and then microscopic examination of the sputum will reveal cancer cells. But we have already indicated that absolute reliance cannot be placed on either positive or negative cytologic findings.

The roentgen-ray findings in these cases are also not uniformly diagnostic. In some cases the picture is that of pulmonary tuberculosis or abscess. Figures 21 to 23 show roentgengrams of a case in which we diagnosed abscess clinically. Examination of the pus drawn with an aspirating needle showed neoplastic cells. Injection of a solution of methylene blue colored the sputum immediately. However, the diagnosis must be made clinically; roentgenologically too many failures will be reported.

There is one form of cancerous abscess of the lung which can be diagnosed only with the aid of the roentgen rays. It occurs in the center of a lobe, presumably being derived from the epithelium of the smaller bronchi or alveoli and not from the more common origin of the larger bronchi or bronchial mucous glands. It appears that the neoplasm breaks down quickly in these cases, either as a result of lack of nutrition owing to outgrowing the blood supply or because of secondary infection. At any event, the broken down neoplastic tissue is expectorated, leaving a larger or smaller cavity surrounded by a thin wall. As will be seen from the roentgenograms (figs. 21 to 22), the cavity may be completely or partly filled with secretions. Giving the patient a large dose of an opiate in the evening will result in his retaining the secretions in the cavity and the next morning the roentgenogram will show the cavity filled. In two cases of somewhat similar cavities the upper lobe of the lung was completely excavated and filled with secretions. It will be noted that the lower margin of the abscess corresponds to the interlobar fissure which prevents for a time the extension of the tumor. However, later on the growth invades the lower lobe (figs. 23 and 24).

This type of neoplastic disease of the lung can best be diagnosed with the aid of the roentgen rays. However, an echinococcus cyst gives a

similar roentgenogram and the symptomatology may not be unlike that of cancerous abscess. Finding of the scolices, hooklets or cyst membrane in the sputum, eosinophilia, and perhaps a hydatid cyst in the liver or elsewhere, as well as the complement fixation test for echinococcus disease will differentiate it from cancer.

DURATION OF LIFE

Primary cancer of the lung is not as rapidly fatal as carcinoma of most other organs. While we have seen some cases that terminated fatally in less than six months after the appearance of the first symptoms, the majority lasted more than one year. One patient lasted four years and I have seen a patient with sarcoma of the lung who lived for five years after the onset of the disease. It is noteworthy that there may be remissions in the progress of the disease during which the patient feels comparatively well for weeks or months. In several cases the growth remained stationary in size and no metastases occurred, the patients feeling well and even gaining in weight and strength considerably, and we began to suspect the reliability of the diagnosis. But later on the neoplasm broke down, sent out metastases and the course was rapidly downward. This point is to be borne in mind when rendering clinical judgment in cases of neoplastic disease of the lung.

THE DIAGNOSTIC AID IN EVALUATING THE VIGOR OF INSPIRATORY COSTAL EXCURSION*

C. F. HOOVER, M.D.
CLEVELAND

The vigor with which the arches of the ribs move in an inspiratory direction is determined by the excess of inspiratory force of costal movement over the counterbalancing or restraining agencies that retard the movement of the ribs.

In inspiration the thorax is enlarged circumferentially and longitudinally by the scaleni and the intercostal muscles and the diaphragm. The muscles that increase the circumference of the thorax (the scaleni and intercostals) and the diaphragm, which increases its length, must mutually counterbalance and overcome each other. To appreciate this fundamental and important fact, one should study a patient in whom paresis of all these muscles is sufficient to preclude their action in concert but which still affords sufficient power to enable them to function separately.

Such a patient recently entered the women's ward at Lakeside Hospital. She was 40 years old and had a chronic poliomyelitis anterior that involved all the neck muscles, the intercostals, and both forearms, thighs and legs. All the neurologic symptoms were motor and trophic. There were no symptoms of sensory impairment. As the patient lay in bed, quietly breathing twenty times a minute, the entire thoracic cage moved in an expiratory direction during inspiration as the abdomen was protruded by phrenic excursion. The manubrium and all the ribs moved caudad in inspiration, and the costal margins moved mediad. When the patient was watched for a time, it was observed that occasionally (about every tenth inspiration) she enlarged her thorax circumferentially but never on these occasions was there any evidence of phrenic excursion. It was apparent that in automatic respiration the muscles that enlarged the circumference of the thorax and the diaphragm, which enlarged its length, had sufficient power to function singly but not in unison. When instructed to take a deep breath, the patient either lifted and enlarged the circumference of the thorax without increasing the length or she increased its length by abdominal breathing without increasing its circumference. In other words there was sufficient strength in the scaleni and intercostal muscles to overcome the retractility of the lungs when unopposed by the diaphragm.

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* From the department of medicine of Western Reserve University at Lakeside Hospital.

* Read at the meeting of the Association of American Physicians, Washington, D. C., May, 1925.

and the lungs could be extended by the diaphragm when unopposed by the scaleni and intercostal muscles. Her expected vital capacity when she was lying down was 3,700 cc., but she could never show a vital capacity above 1,400 cc. This patient shows in a striking way how the inspiratory function is impaired when there is sufficient muscular vigor to overcome the retractility of the lungs but not enough to maintain the normal reciprocal counterbalancing between the scalenocostal and the phrenic forces. In this case the want of costal force of excursion was clearly shown to inspection as well as to palpation. In many other cases, however, we have to deal with other counterbalancing factors that reduce the vigor of costal excursion in one entire side or a part of one side, when the visible delay or diminution of excursion is imperceptible but the lessened force of costal excursion as perceived by the palpating fingers is pronounced.

Every experienced examiner must often have perceived how much more distinctly he could palpate than see a disparity in excursion in symmetrical chest regions. This disparity is not due to a more delicate perception by the hand of differences in time or distance of excursion but to the perception of the comparative force of excursion. If one directs his attention to the comparative force of excursion, evidence will be got for disturbances in pulmonary ventilation that quite escape inspection.

STENOSIS OF A BRONCHUS

There may be considerable stenosis of the main bronchus to a lung that will yield no other physical sign than diminished force of costal excursion on the affected side. Percussion resonance may be unchanged. Auscultation may reveal no diminution in the intensity of the transmitted respiratory or vocal sounds, and even the palpable vocal fremitus may not be lessened, although the coarse palpable vibrations may be diminished by a moderate degree of bronchial stenosis that will not impede the transmission of audible sounds.

Inspection may not reveal a disparity in excursion, but the palpable lessened force of excursion is clearly perceived.

REPORT OF CASE

A patient who had an aneurysm of the transverse aortic arch showed no signs to percussion, inspection or auscultation. However, when the ear was applied over the region of the transverse arch, a deep systolic impulse and a diastolic impact were detected. There was no visible disparity in the extent of excursion of the two sides, but when a vigorous inspiratory effort was made, the lessened vigor of excursion on the left side was pronounced. An attempt to restrain the upper right ribs in their movement in a cephalic direction was ineffectual, but when the examining fingers were hooked over the upper borders of the ribs in the midclavicular and axillary lines of the left side, the costal excursion could be restrained and the force of their excursion was lessened to a marked degree.

The use of the fluoroscope confirmed the diagnosis, but the impaired vigor of costal excursion was the weightiest physical sign brought out by objective examination.

The same sign was often observed in other thoracic diseases, but there was no way in which the disparity in the vigor of costal excursion could be recorded or evaluated. In unilateral bronchial stenosis, however, it seemed possible to arrive at a mathematical comparative evaluation of the effects on the time and on the vigor of excursion of the affected side. It is obvious that if one bronchus has its lumen reduced one-half and the distensibilities of the lungs are equal, then, assuming the activation strength of the inspiratory muscles on the two sides to be equal, the side with the narrowed bronchus must move with a diminution of vigor that is determined by the degree of stenosis. So will the affected side attain a lesser expansion, which can be expressed by the prolongation of time that would be required to attain a normal distention of the lung with the stenosed bronchus. The lessened vigor of excursion can be expressed mathematically by determining how much more the barometric pressure must be lowered on the side of the narrowed bronchus to counterbalance the resistance of the bronchial stenosis; or, in other words, how much greater suction must be employed on the side of the narrowed bronchus to give the same vigor of excursion as exists on the opposite normal side. This difference in vigor of excursion is perceptible only to palpation. The delay in time of excursion is perceived by inspection.

The following problem was presented to a consulting engineer, Victor Phillips, who kindly gave me the method of its solution employed in engineering when the transmission of air pressure is used.

Problem.—If a normal man is able to inhale 4,000 cc. of air in one second and then the bronchus of one side has its lumen narrowed from 0.8 cm.^{2} to 0.4 cm.^{2}, how much will the pleural suction on the affected side have to be increased to provide it with a volume flow per second of 2,000 cc. of air? Also, how much will the time of inspiration have to be prolonged to procure a flow of 2,000 cc. through the narrowed bronchus if the pleural suction remains the same on both sides?

The answer to the first problem gives us a mathematical expression of the palpable loss of vigor of costal excursion on the side with the bronchial stenosis, and the answer to the second gives a mathematical interpretation to the visible delay in costal excursion. The solutions of the two problems show that the suction would have to be increased 185 per cent, whereas the time factor would have to be increased only 67 per cent. These results strikingly contrast the palpable with the visible evidences for restraint to pulmonary excursion from bronchial stenosis. In other words, we palpate the 185 per cent and see the 67 per cent.

The pressure drop (or gradient) necessary to force a gas through an orifice or tube varies with the square of the velocity of the gas. It follows, therefore, that even a small restriction in one of the bronchi alters materially the normal pressure relations governing the flow of air into and out of the lungs. How great may be the unbalancing effect between the two lungs by a restriction in one of

the bronchi may be strikingly illustrated by the well known laws of physics for the flow of gases. The general relationship may be expressed: $h = \frac{K}{C} 2 \times \frac{V^2}{2g}$

in which

h = the pressure drop through that part of the bronchus under consideration (millimeters of mercury).

V = air velocity at the same point (feet per second).

C = a constant expressing the resistance or friction of the same part of the bronchus.

K = a constant calculated from the temperature of the air and the atmospheric pressure.

g = the accelerative force of gravity (feet per second).

Let it be assumed that the normal of the two bronchi has a sectional area of 0.8 cm.^{2} and the restricted bronchus an area of 0.4 cm.^{2}. Assume further a normal inhalation of 2,000 cc. of air in one second to each lung (72 F. and 29.92 pounds atmospheric pressure). The effect of the restriction of area from 0.8 to 0.4 cm.^{2} may then be calculated rather precisely. Limiting consideration to a short length of the bronchus, say 1 inch (2.5 cm.), within which length the restriction in question will be entirely contained, then for the conditions assumed in the foregoing the *normal* pressure drop through the 1 inch of bronchus will be 3.5 mm. of mercury. If the other lung is to inhale this *same volume* of air in the *same space of time*, then the pressure drop through the corresponding 1 inch of bronchus in which the restriction exists will be 31.2 mm. of mercury. Since for this condition (of equal volumes in the same time to both lungs) the pressure drops through the other parts of the trachea, bronchi and bronchial tubes will not be affected by the restriction, it follows that $31.2 - 3.5 = 27.7$ mm. of mercury is the increased drop or suction that must be produced by the muscular action of the chest walls in order to make both lungs function alike. Suppose, now, that the normal pressure difference between atmosphere and the pleural cavity is 15 mm. of mercury, then it is apparent that the foregoing "drag" on the chest walls would be increased on the restricted side to a total of 42.7, or nearly three times the "drag" on the normal. The exact amount of this increase in drag in any particular instance will, of course, vary materially not only with the amount of the restriction, but also with the shape and character of the restriction which will determine the friction constant (C) referred to above. The constants used in the foregoing calculations are those used in engineering for restricted tubes sufficiently similar to the bronchi to render the results comparatively accurate.

As a matter of fact, the same volume of air would not be inhaled through the restricted bronchus as through the normal bronchus *in the same length of time*. Some further idea may therefore be had as to the effect of restriction by calculating the additional time necessary to inhale the same volume of air if the pleural cavity suction is the same for both lungs. In the first example the time for inhaling 2,000 cc. into each lung was 1 second and to accomplish this required nearly three times the suction on the restricted side, or more precisely an increase of 185 per cent over that on the normal side. With the *same suction* on both sides, the other conditions remaining unchanged, there would be required 1.67 seconds to inhale the same volume through the restricted bronchus as against 1 second for the normal bronchus, an increase of 67 per cent. In other words, the condition of restriction in one bronchus is more strikingly apparent in what may be termed the drag against which the chest walls must act than it is expressed in terms of time delay. That this is true may be briefly restated as follows: Pressure drop increases with the square of the velocity, whereas time of inhalation varies inversely with the first power of the velocity.

When thus mathematically expressed, we see why the vigor of excursion is such a delicate measure of the drag or counterbalance on the inspiratory excursion of a lung. There is no method by which this

disparity in vigor of excursion can be quantitatively estimated. It can be clearly evaluated by manual examination, but no instrument of precision can be employed.

In several former articles I have interpreted and explained the significance of asymmetry in the excursion of the costal borders. Further observations on this subject lead to the conviction that the comparative vigor of excursion of the costal borders is a more delicate test than the comparative extent of excursion. The delicacy of this test is shown by the fact that in normal subjects the subcostal angle widens symmetrically with inspiration, but the left costal margin moves normally with less vigor than the right. The reason for this is the fact that the subcardial diaphragm to the left of the median line is slightly less convex than to the right. The difference in convexity under normal conditions is not sufficient to cause asymmetry in extent of excursion of the two inner halves of the costal margins, but the less vigorous excursion on the left is clearly perceived if the two borders are alternately restrained during forced inspiration. It will be perceived that the left moves with less vigor under the restraining hand than the right. By comparing the vigor of lateral movement of the inner and outer halves of a costal margin or symmetrical parts of opposite sides we can obtain a clear perception of the comparative drag on the lateral movement of the costal ends that originates from disparity in convexity of the diaphragm of the two sides.

PARESIS OF THE INTERCOSTAL MUSCLES OF ONE SIDE

In hemiparesis of cerebral origin or in regional disease of the spinal cord, the vigor of costal excursion is lessened as well as the vigor of movement of other skeletal muscles. It is not detected when only the extent of costal movement is observed and the vigor of movement is neglected. The intercostals have a bihemispherical supply quite like the frontalis.

The familiar method of differentiating a supranuclear from a nuclear or infranuclear facial palsy is to determine the share of the frontalis in the paresis. We find, however, that, although the forehead may be symmetrically wrinkled in cases of cerebral facial paresis, the wrinkles are not so firmly held against a smoothing pressure on the affected side. It is exactly the same with the intercostal muscles.

In some cases of cerebral palsy the thorax of the affected side can be seen to have a diminished extent of excursion; in other cases the two sides are seen to move symmetrically. But in all cases of complete cerebral hemiparesis or when the upper and lower extremities of one side are involved, the vigor of costal excursion is diminished on the affected side. The neurologists have differed in their opinions on this subject because they have observed only the extent of costal movement.

It is true that in many cases the extent of excursion is symmetrical on the two sides, but if the patient makes forced inspirations and the vigor of costal movement on the two sides is alternately compared, the ribs on the paretic side will always be found to move with less vigor. There may be sufficient strength on the affected side to compress and expand the lung to its maximum capacity or so nearly to it that an examiner will be in doubt about lessening of the vital capacity. The limit of pulmonary expansion is not determined by the strength of the respiratory muscles but by the maximum extensibility of the visceral pleura and pulmonary parenchyma. There may be quite enough strength in the paretic intercostal muscles to contribute their adequate share to expansion and compression of the lungs, but when compared with the normal side the ribs on the paretic side will always be found to move with less vigor against resistance.

In cases of cord syphilis and syringomyelia, the paresis of intercostal muscles may not be sufficient to lessen the extent of costal excursion, but when the upper ribs are suspected of involvement the vigor of excursion should be tested by hooking the fingers over the upper borders of the ribs in an effort to restrain their cephalad movement in a forced inspiration. Paresis of the lower five intercostal muscles should be tested by palpating the vigor with which the outer half of the costal margin moves laterad in a forced inspiration.

In cases of transverse myelitis or cord tumor, the vigor of movement of the ribs aids in localizing the upper limits of the lesion. I recently saw a patient who had a complete sensory and motor paraplegia inferior. The upper limit of the anesthesia was in the sixth intercostal space. When the patient made a series of forced inspirations it was found that the sixth ribs moved with a vigor that could not be restrained, whereas the seventh ribs could easily be restrained in their cephalad movement. A moderate amount of practice enables one to recognize which ribs are moved by paretic intercostal muscles.

The disparity between the visible and palpable evidences for counterbalancing of the force of inspiratory thoracic excursion is just as pronounced when resistance to lung extension lies in diminished extensibility from disease of the lung or visceral pleura. Nearly all the physical signs we employ in studying the lung are directed toward detection of changes in its size, density and extensibility, but extensibility is the first physical attribute to be affected in any disease of the bronchi, parenchyma or visceral pleura, and the most sensitive test that can be employed to detect the counterbalancing of lung resistance to the force of extension is to study the comparative vigor of costal excursion over symmetrical regions.

Incipient tuberculosis of the lung will affect the vigor of costal excursion over the site of its location when inspection, percussion, pal-

pation and the roentgen ray fail to give any evidences. It is therefore of great assistance in the early diagnosis of tuberculosis of the upper lobes of the lung to compare the vigor of costal excursion on the two sides over the second, third and fourth ribs. This should, of course, always be done when the patient is recumbent, so that there may be no restraint to costal excursion from the abdominal muscles.

I have frequently been able to detect a lessened vigor of excursion in the upper ribs in patients who had no other symptom than hemoptysis when all other methods of examination failed to indicate which was the affected side.

In former years the functions of the scaleni and intercostal muscles and the diaphragm were so misconceived that an analytic examination of thoracic excursion was impossible. To make a critical examination of respiratory excursion is obligatory on the internist, neurologist and surgeon, because it yields valuable information in the study of medical and surgical diseases of the thorax and upper part of the abdomen, and also in diseases of the brain and spinal cord. When we study the counterbalancing between the force of costal excursion and extensibility of the lung, we gain information about a physical attribute of the lung, which is most sensitive to all its pathologic lesions, and reciprocally we also have a sensitive method for detecting impairment in the nerve supply to inspiratory muscles.

SUMMARY

When the action of the inspiratory muscles is (in a pulmonary region) opposed by some other factor than the normal retractility of the lung, or when there is a regional paresis of intercostal muscles, the vigor with which the ribs concerned move in an inspiratory direction offers a more delicate method for detecting the counterbalancing of the costal excursion than does inspection of the extent of excursion. The added drag that is perceived by palpation can be expressed by a mathematical formula when stenosis of one large bronchus is concerned. The lessened vigor of excursion of the ribs in any region will give evidence for any lesion that may diminish the extensibility of the underlying lung when the extent of excursion may reveal no evidence and when percussion and auscultation reveal no evidence for diminished resonance or increased density of the lung and when adventitious ausculatory signs are wanting. Diminished vigor of excursion of ribs should be studied in a routine manner because the vigor of costal excursion over any pulmonary region accurately mirrors the extensibility of the underlying lung. Because extensibility is the first attribute affected in all pulmonary diseases, any impairment of this attribute offers the earliest procurable evidence for regional lung disease.

CORRIGAN'S DESCRIPTION OF AORTIC INSUFFICIENCY

EDITED, WITH A NOTE

LOGAN CLENDENING

KANSAS CITY, MO.

[NOTE.—Sir Dominic John Corrigan, the author of the marvelous record of clinical observation reprinted below, was according to the *Lancet's* notice at the time of his death "a perfect Irishman." He practiced medicine during most of his life in Dublin, a dominant member of that brilliant group of physicians who resided there in the early part of the nineteenth century—Graves, Stokes, Robert Adams, William Wallace, who first popularized the use of iodide of potash, and Francis Rynd, the inventor of the hypodermic, being his colleagues, and John Cheyne and Colles of a slightly earlier generation.

It is worth noting that he puts himself down as one of the physicians to the Charitable Infirmary, Jervis Street, Dublin. This hospital had beds for only six patients at a time, and this scanty material was probably the basis for Corrigan's observations which led to the accurate account of the pulse signs and other phenomena of aortic insufficiency.

He was born in 1802, six years after Graves and two years before Stokes. He received his medical education at Sir Patrick Dun's Hospital, afterward matriculating at the University of Edinburgh where he received his doctor of medicine degree in 1825, returning to Dublin to take up active practice.

The paper from which he derives most of his fame was published, as can be noted below, in the *Edinburgh Medical and Surgical Journal* in 1832. His later description of fibroid phthisis, or as he called it "cirrhosis of the lung," attracted perhaps even more attention in his life time. He had an enormous fame in his own day both as a lecturer and as a consultant, and he used to tell, with great unction, how he had to have a secret doorway built in his house in order to escape from the throngs of patients. After playing an important part in the handling of the Irish famine fever in 1847 and serving some terms in Parliament he died in 1880. The most easily obtainable sketch of his life is probably in Walsh's "Makers of Modern Medicine," Fordham University Press, New York, 1907.

The best introduction to his character and labors is to be found in the appended article. "The superb plate," to use the words of Dr. Fielding Garrison, accompanying the original paper is reproduced from a photograph. Two final comments may be made. First, the work of the great Irish school is a fine appendage to Laënnec's introduction of the stethoscope. Laënnec's interest was centered on the lungs; the portions of his book dealing with the heart are plainly inferior. But the extension of the use of the stethoscope to heart disease was worked out, to no minor extent, by the Dublin group. Second, this paper is reprinted because the medical journal in which it appeared is far from easy of access to most students of medical history in this country. Up to the end of the eighteenth century when a man had a medical observation to make he usually published it in a book. These books, such as Jenner's "Inquiry" and Withering's "Account of the Foxglove," turn up at booksellers every once in a while and are fairly well distributed in libraries, private or public. But with the beginning of the practice of publication in circulating magazines, the great original clinical descriptions of diseases are more and more likely to be out of the student's reach and for that reason should be reprinted from time to time.

Aortic valve disease had been described before Corrigan by Cowper, Vieussens and Hodgkin, but he gave the first account of the arterial signs.]

ON PERMANENT PATENCY OF THE MOUTH OF THE AORTA OR INADEQUACY OF THE AORTIC VALVES

D. J. CORRIGAN, M.D. One of the physicians to the Charitable Infirmary, Jervis Street, Dublin; lecturer on the theory and practice of medicine; consulting physician to St. Patrick's College, Maynooth, Ireland.

(*From the Edinburgh Medical and Surgical Journal*, April 1, 1832)

The disease to which the above name is given has not, so far as I am aware, been described in any of the works on diseases of the heart. The object of the present paper is to supply that deficiency. The disease is not uncommon. It forms a considerable proportion of cases of deranged action of the heart, and it deserves attention from its peculiar signs, its progress, and its treatment. The pathologic essence of the disease consists in inefficiency of the valvular apparatus at the mouth of the aorta, in consequence of which the blood sent into the aorta regurgitates into the ventricle. This regurgitation, and the sign by which it is denoted, are not necessarily connected with one particular change of structure in the valvular apparatus, and hence the name, "Permanent Patency of the Mouth of the Aorta, or Inadequacy of the Aortic Valves," has been chosen as simply expressing such a state of the parts as permits the regurgitation to occur.

I have been in the habit for some years of describing this disease under the name of inadequacy of the aortic valves; but Dr. Elliotson, in his elegantly written work on diseases of the heart, has given to a somewhat analogous morbid state of the auriculoventricular opening a better name, permanent patency. I have, for this reason and for the sake of uniformity, adopted the term, and I shall continue to use it as synonymous with my own term, inadequacy of the aortic valves.

The morbid affections of the valves and aorta permitting this regurgitation are the following:

First, the valves may be absorbed in patches, and thus become reticulated and present holes, through which the blood flows back into the ventricle.

Second, one or more of the valves may be ruptured; the ruptured valves, when pressed, flopping back into the ventricle instead of catching and supporting the column of blood in the aorta, the blood then regurgitating through the space left by the broken valves.

Third, the valves may be tightened or curled in against the sides of the aorta, so that they cannot spread across its mouth, and an opening is then left between the valves, in the center of the vessel, through which the blood flows freely back into the ventricle.

Fourth, the valves without any proper organic lesion may be rendered inadequate to their function by dilatation of the mouth of the aorta. The aorta, affected by aneurysm, or dilated, as it frequently is in elderly persons about its arch will sometimes have the dilatation extend-

ing to the mouth of the vessel, and in such a case, the valves become inadequate to their function, not from any disease in themselves, but from the mouth of the aorta dilating to such a diameter as to render the valves unable to meet in the center: the blood then, as in the other instances, regurgitates freely into the ventricle.

GENERAL SYMPTOMS

On the general symptoms that accompany this disease, little is necessary to be said. Like most of those connected with affections of the respiratory and circulating organs, they are uncertain and unsatisfactory. There are frequently convulsive fits of coughing, more or less dyspnea, a sense of straitness and oppression across the chest, palpitations after exercise, sounds of rushing in the ears, and inability to lie down. Neither one nor all of these symptoms are essential to the disease. They may all arise from varied affections of the lungs, heart, liver or nervous system. They neither tell us the seat of the disease nor the extent of the danger.

SIGNS

What is deficient in general symptoms from their obscurity is, however, amply supplied by the certainty of the physical and stethoscopic signs, which may be referred to the three following indications: (1) visible pulsation of the arteries of the head and superior extremities; (2) bruit de soufflet and frémissement, or a peculiar rushing thrill felt by the finger, in the carotids and subclavians. In conjunction with these may be reckoned the pulse, which is invariably full. When a patient affected by the disease is stripped, the arterial trunks of the head, neck and superior extremities immediately catch the eye by their singular pulsation. At each diastole the subclavian, carotid, temporal, brachial, and in some cases even the palmar arteries, are suddenly thrown from their bed, bounding up under the skin. The pulsation of these arteries may be observed in a healthy person through a considerable portion of their tract, and become still more marked after exercise or exertion; but in the disease now under consideration, the degree to which the vessels are thrown out is excessive. Though a moment before unmarked, they are at each pulsation thrown out on the surface in the strongest relief. From its singular and striking appearance, the name of visible pulsation is given to this beating of the arteries. It is accompanied with bruit de soufflet in the ascending aorta, carotids, and subclavians, and in the carotids and subclavians where they can be examined by the finger, there is felt frémissement, or the peculiar rushing thrill, accompanying with bruit de soufflet each diastole of these vessels. These three signs are so intimately connected with the pathological causes of the disease, and arise so directly from the mechanical inadequacy of the valves, that they

afford unerring indications of the nature of the disease. In order to understand their value, it is necessary to consider their connection with the cause by which they are produced. The visible pulsation of the arteries of the neck, etc., may be first examined.

In the perfect state of the mechanism at the mouth of the aorta, the semilunar valves, immediately after each contraction of the ventricle, are thrown back across the mouth of the aorta by the pressure of the blood beyond them, and when adequate to their function of closing the mouth of this vessel, they retain in the aorta the blood sent in from the ventricle, thus keeping the aorta and larger vessels distended. These vessels consequently preserve nearly the same bulk during their systole and diastole. But when the semilunar valves, from any of the causes enumerated, become incapable of closing the mouth of the aorta, then after each contraction of the ventricle, a portion of the blood just sent into the aorta, greater or less, according to the degree of the inadequacy of the valves, returns back into the ventricle. Hence the ascending aorta and arteries arising from it, pouring back a portion of their contained blood, become, after each contraction of the ventricle, flaccid or lessened in their diameter. While they are in this state, the ventricle again contracts and again impels quickly into these vessels a quantity of blood which suddenly and greatly dilates them. The diastole of these vessels is marked by so sudden and so great an increase of size as to present the visible pulsation which constitutes one of the signs of the disease.

That this visible pulsation of the arteries is owing to the mechanical cause here assigned is made evident by several circumstances. It is most distinct in the arteries of the head and neck, which empty themselves most easily into the aorta, and of course into the ventricle. In the arteries of the lower extremities, of even larger size than those which present it above the head and neck, it is not seen to any comparative degree, and most generally not at all while the patient is standing or sitting. It is much more marked in arteries of the head and neck in the erect than in the horizontal posture; and a patient suffering under the disease himself first pointed out a circumstance which is convincing of its being produced as asserted. He could increase the pulsation of the brachial and palmar arteries in a most striking degree by merely elevating his arms to a perpendicular position above his head. He thus enabled the brachial and palmar arteries to empty themselves more easily back upon the aorta. They became more flaccid, and then, on the next contraction of the ventricle, their diastole became comparatively greater, and their visible pulsation, of course, more marked. The same effect could be produced in the arteries of the lower extremities by lying down and elevating the legs on an inclined plane. The strength of the heart has little to do in producing this singular pulsation for it is

never observed in an equal degree, and most generally not at all, in the arteries of the lower extremities.

If it be asked, is the explanation here adduced of the cause of this visible pulsation sufficient to account for its appearance in the brachial and radial arteries, since the blood to return back from these vessels into the arch of the aorta should flow upwards when the patient holds his arms in the ordinary position, flexed or hanging by his side, the following reply may be made: When the subclavians are pouring back their blood into the arch of the aorta and ventricle, the elasticity of the brachial arteries acting upon the blood just urged into them, forces it back along with the retrograde current of the subclavians, no obstacle meeting it in that direction. The brachial arteries thus partially empty themselves and become in their systole of a lessened diameter, like the carotids and subclavians, but in less degree. The next jet of blood from the ventricle dilates them, and as in the subclavians, produces in them a visible pulsation; and if they be assisted in returning their blood by elevating the arms to a perpendicular position, their pulsation becomes, as has been already observed, much more strongly marked. The arteries of the lower extremities are not similarly circumstanced. The arteries of the upper extremities are assisted in emptying themselves back towards the heart, by the retrograde current in the subclavians and ascending aorta; but on the blood contained in the arteries of the lower extremities, the tall column of blood in the descending aorta is pressing, and prevents any return; or if it be supposed that of the large mass of blood in the descending aorta, a small portion flows back into the arch, it can produce little change in the contents of the iliacs and femorals; and moreover, whether the column of blood in the aorta be lessened or not in diameter, the pressure on the contained blood of the iliacs and femorals will remain the same, and keep these vessels distended. If we, however, as already observed, alter the relation of the several arteries to the arch of the aorta, so as to facilitate the reflux of their contained blood, for instance, from the radial arteries, by raising the arms to a perpendicular line above the head, from the iliacs and femorals by placing the patient in a recumbent posture and raising the legs upward on an inclined plane, the visible pulsation becomes much more marked in these respective arteries.

The bruit de soufflet, which is heard in the ascending aorta, carotids and subclavians with the accompanying frémissement in the latter arteries is next to be considered. The bruit de soufflet characterizing this disease is heard, as already observed, in the ascending aorta, its arch, and in the carotids and subclavians. It can be followed upwards from the fourth rib along the course of the aorta increasing in loudness as it ascends, until it is heard of great intensity in the upper part of the

sternum, where the arch of the aorta most nearly approaches this bone, and then branching to the right and left, it can be traced into the carotids and subclavians of both sides; and in these trunks it assumes a harshness that it did not possess in the aorta. This bruit de soufflet is synchronous with the visible pulsation, with the diastole of the arteries. It is of no consequence whether the ascending aorta and its large branches be sound or be diseased; this bruit de soufflet is as loud in the one case as in the other. To account for the presence of this sign, and why it extends so far from the seat of the disease and along sound vessels, it is necessary to refer to a paper published in the *Lancet* of 1829, volume 2, page 1. Continued observations from the date of that paper to the present have confirmed the view then taken of the cause of that singular sound; of its being dependent purely upon a physical cause, on a mechanical change in the manner of the blood's flowing.

In that paper is related an experiment, which may be well to recapitulate here. A flexible tube, such as a piece of small intestine, or a portion of artery is connected by one end with a tube which has a current of water of considerable force running through it. While the piece of intestine or artery is kept fully distended by the supply of water from the tube no sound is produced by the motion of the fluid; but if the flexible tube, while the fluid is moving through it, be pressed upon in any part, so that the quantity of fluid passing through the contracted part is no longer sufficient to keep the further portion of the tube tense, then, beyond the contracted part, where the tube is less tense, or in some degree flaccid, a distinct, and, according to the velocity or force of the current, a loud bruit de soufflet is heard; and, at the same time, if the finger be gently laid on the part of the tube where the bruit de soufflet is heard, a slight trembling of the tube is perceived, evidently arising from the vibrations into which the current within is throwing its sides. If in place of constricting any one part of the flexible tube, the whole tract of tube be allowed to become partially flaccid, by diminishing the supply of fluid, and the fluid be then allowed to rush along the tube by jets, at each jet the tube is suddenly distended, resembling the visible pulsation described above; and with each diastole of the tube, there is a sudden and loud bruit de soufflet, and, synchronous with the bruit de soufflet there is frémissement felt by the finger.

Both the sound heard and the sensation felt by the finger in this experiment may be explained by the principles which regulate the motion of fluids. It may be remarked that it is a property of fluid in motion that, when discharging itself from the orifice of a tube into open space, or into a vessel of wider capacity not fully distended, its particles move in lines from the orifice, like so many radii tending to leave vacuums between them. When the flexible tube, artery or intestine, therefore, is kept fully distended, the fluid moves forward as a mass,

there is no tendency in its particles to separate one from another—they all press equally—there is no vibratory motion of the sides of the tube, and consequently no sound, and no frémissement or trembling. But if the tube be not kept fully distended, then the fluid propelled through it rushes along as a current; and its particles tend to leave particles between them, throw the sides of the tubes into vibrations, which can be very distinctly felt by the finger, and which give to the ear the peculiar sound bruit de soufflet, and to the touch frémissement.

These principles may be applied to the state of the ascending aorta and its branches in the instances before us. When the aortic valves are fully distended to their function of perfectly closing the mouth of the aorta, and preventing any regurgitation of blood, the aorta and its branches are kept fully distended, the blood is at each contraction of the ventricle propelled forward *en masse*, and there is no trembling or vibratory motion of the sides of the aorta, carotids and subclavians, and, as in the flexible tube when fully distended, no sound is emitted. But when the valves, having become inadequate to their office, permit some of the blood contained in the ascending aorta, carotids and subclavians to return to the left ventricle after each contraction then the aorta and the trunks become, like the flexible tube in the second part of the experiment partially flaccid, and at the next contraction of the ventricle the blood propelled into them is sent along as a rushing current, which throws the sides of these arteries into vibrations, and these vibrations give to the ear bruit de soufflet and to the finger frémissement. These two signs may be traced to a varying distance from the mouth of the aorta and always along the carotids, and to the outer third of the subclavians, and sometimes in the brachial arteries, as far as the bend of the arm, the distance to which they are heard being determined by the limit to which the current-like motion of the blood producing them is extended. In those cases in which the deficiency of the valves is considerable, allowing a full stream of blood to rush back into the ventricle, there is heard in the ascending aorta a double bruit; the first accompanying the diastole of the artery, the second immediately succeeding; and in listening to the two sounds, constituting this double bruit de soufflet, the impression made distinctly on the ear is that the first sound is from a rushing of blood up the aorta, the second from a rushing of it back into the ventricle. It is impossible for those who have not heard this double bruit to conceive the distinctness with which the condition described is made on the ear. A patient in one instance heard the double sound distinctly in his own person, and referred it to its cause, a rushing of blood from and to the heart. The bruit de soufflet and frémissement are not perceived in the arteries of the lower extremities, when the patient is in the sitting or standing posture. The pressure of the blood in the abdominal aorta is sufficient in these postures to keep

the vessels arising from it fully distended, and thus no vibratory motion of their parietes being permitted, there is no bellows sound, nor frémissement or rushing thrill.

HISTORY AND PROGRESS OF THE DISEASE

Of eleven cases of the disease, only two occurred in females, and in both of these the valves were nearly quite sound in texture: but the aorta being thinned and dilated, the valves could not meet so as to prevent regurgitation. None of the cases occurred in very early age. The youngest person presented laboring under the disease was 20 years of age. In this respect, inadequacy of the aortic valves differs from narrowing of the left auriculoventricular opening which is not infrequently met with in children, and even in infants at the breast. The causes of the disease are uncertain. In one case the disease followed an attack of acute rheumatism which had been accompanied by symptoms of pericarditis. In some cases the commencement of the disease was referred by the patient to an inflammatory affection of the chest, which had occurred months or years before, while in other cases no cause or date could be assigned.

The symptoms accompanying its commencement and progress are very variable. Most generally the patient describes the first sensations as having been a feeling of oppression and straitness across the chest, with palpitation of the heart on unusual exercise. These symptoms become gradually more distressing, and are after a very uncertain period of time accompanied by fits of coughing resembling paroxysms of asthma, and terminating in scanty expectoration. In a few cases, however, cough was not at any time, even up to the last hours of life, an urgent symptom: the oppression and straitness of the chest, with palpitation on any exertion, and an anxiety for a supply of fresh air being the principal complaints. As the disease proceeds, the straitness and oppression about the chest become more distressing, fits of coughing more frequent, and the patient has an anxiety, approaching to agony, for a free supply of fresh air, frequently starting from bed at night under the dread of suffocating. In the last stage the state of suffering is extreme. The patient will not lie down for a moment, from the dread of suffocation. The face which had been pale becomes purple on the lips as in suffocative catarrh; edema of the legs comes on, followed ultimately by edema of the hands and arms; there is no sleep, or there are almost incessant startings from it; the countenance assumes a most painful expression of sinking; and the patient at length dies exhausted. The pulse in no case was under 80. It ranged from that to 110, and in every case it has been all through the disease (unless influenced by medicine) full and vibrating, even to within a few hours of death.

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The duration of the disease is very uncertain. No case was of less duration than two or three years, and some of the cases at present under treatment have been of seven or eight years' standing. The time which the disease may continue without terminating fatally seems to depend principally upon the extent to which regurgitation is permitted. The case in which the valves from small perforations allowed but little regurgitation continued for many years, while the case which furnished plate 2 and in which the valves were ruptured and much injured, allowing considerable regurgitation, terminated fatally in less than three years.

DIAGNOSIS

Inadequacy of the aortic valves may be confounded with narrowing of the mouth of the aorta, either congenital or from diseased valves, with disease of the auriculoventricular valves, with aneurysm of the arch of the aorta, or arteria innominata, with nervous palpitations and with asthma. Congenital narrowing of the mouth of the aorta is a very rare disease, but narrowing of the mouth of this vessel produced by vegetations on the valves is not unusual; and bruit de soufflet is a sign common to it, and to the disease we are considering. The resemblance between the signs of the two diseases extends, however, no further. The middle pulsation of the arteries arising from the arch of the aorta, which forms so striking a sign of inadequacy of the aortic valves is wanting in narrowing of the mouth of the aorta. The pulse is also strikingly different in the two diseases. In narrowing of the aortic orifice it is small and contracted; in inadequacy of the aortic valves it is invariably full and swelling. In narrowing of the aortic orifice there is generally a marked contrast between the pulse and the impulse of the heart. The pulse is small and contracted; the impulse of the heart is strong and energetic. In the disease we are considering when there is a contrast it is always in the inverse way, for while the arteries beat with violence, and the pulse is strong and full, the impulse of the heart is scarcely perceptible. When the initial valves becoming indurated or ossified produce narrowing of the auriculoventricular opening, that narrowing produces bruit de soufflet, and the bruit de soufflet thus produced might be confounded with the accompanying inadequacy of the aortic valves. Independently of the visible pulsation of the arteries and the state of the pulse, which accompany inadequacy of the aortic valves, stethoscopic examination points out with certainty the distinction of the two diseases. When the bruit de soufflet is produced by narrowing of the auriculoventricular opening it is heard loudest just where the impulse of the heart against the side is felt. In inadequacy of the aortic valves the converse holds. For over the point where the impulse is or should be felt, bruit de soufflet is either not heard at all or is heard very indistinctly; but as the stethoscope is moved upwards from the heart in a line corresponding

with the ascending aorta, the bruit de soufflet is heard growing louder and louder, until over the arch of the aorta, and in the large trunks arising from it, the sound grates upon the ear with harshness.

Permanent patency of the mouth of the aorta may be mistaken for aneurysm. If the arch of the aorta and arteria innominata approach more nearly than usual to the notch of the sternum, the visible pulsation at the root of the neck becomes so prominent as to lead to a supposition that there is aneurysm, and even of a considerable size, at this part.

Very lately a case came under my observation in which there was a remarkable resemblance to aneurysm. So strong were the pulsations for years in the region of the arteria innominata that until the examination of the body after death there was never even a doubt expressed that the case was not aneurysm. The aorta was thinned and was dilated so much as to render the valves inadequate to their office and leave a permanent patency between them. The arteria innominata, the carotids and subclavians were also dilated beyond their natural size, thus increasing the appearance of the pulsation, but there was no trace whatever of aneurysm in the arteria innominata, such as had been supposed to exist there during life. An acquaintance with the disease under consideration and a knowledge of the fact that a violent throbbing at the root of the neck or notch of the sternum may arise from another cause than aneurysm will prevent the formation of a rash opinion on the cause of the violent throbbing.

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The two diseases, aneurysm of the aorta and inadequacy of the valves, may, however, be combined. . . . The first cases that came under my observation presenting the signs of inadequacy of the aortic valves were cases in which the valves were rendered useless in this way, namely, by the mouth of the aorta sharing in the aneurysmal dilatation. These cases led me into an error; for meeting the signs of permanent patency of the aortic orifice in conjunction with aneurysm, I erroneously attributed to the aneurysm the signs which arose from the permanent patency (vide *Lancet*, Feb. 7, 1829). . . .

Palpitation of the larger arterial trunks, depending on derangements of the nervous system, will sometimes in their violence simulate the visible pulsation arising from inadequate aortic valves; and in females these palpitations will last not only for months but for years, and seem to justify an opinion that there is organic disease of the heart. The nervous palpitation is not, however, accompanied by bruit de soufflet and frémissement, and the absence of these two signs is conclusive as to the nature of the disease. Sometimes, however, more than one examination is required before pronouncing a positive opinion; for in a nervous patient, the alarm excited by the first examination will render the circulation hurried and irregular, and hence there may be in the carotid or

subclavian a momentary bruit de soufflet. In making the examination it is, moreover, necessary that the edge of the stethoscope should not be allowed to press on the artery, because its pressure is sometimes sufficient in those cases to produce the sound. When the bruit de soufflet and frémissement are only momentary no value should be attached to them. In permanent patency of the aorta they are never absent. . . .

TREATMENT

There is no class of disease to which the scientific principles that guide modern medicine have been less applied than to diseases of the heart. . . . With the idea of heart disease is too frequently associated the notion that such disease, without regard to its precise nature or its cause, requires the action and continued enforcement of measures calculated to exhaust strength and depress vital energy, and this error is sanctioned by the standard works on the treatment of heart disease.

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Instead of such treatment, the measures most beneficial are those which by strengthening the general constitution, will give a proportionate degree of vigor to the muscular power of the heart, and thus enable it to carry on the circulation in the absence of that assistance which it ought to receive. With this view a generous and sufficient diet of animal and vegetable food should be advised, at the same time that an abstinence from those beverages, such as malt liquors, which increase much the mass of the fluids, should be enjoined. It is not at all necessary that the patient should be prohibited from attending to his business or profession, provided that he do not devote to it so much attention as to produce debility. And as there is among patients who have learned that they are afflicted with heart disease a universal dread of sudden death it is necessary to undeceive them on this point, and in the present instance it can be done with perfect safety, as the termination of the disease is never sudden.

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Having laid down the plan of treatment proper to be adopted as far as it produces effects upon the system, and through it upon the heart, constituting a part of the system, it now remains to examine the propriety of employing in the disease a remedy such as digitalis, which produces a specific effect upon the heart, rendering its action slow and weak, and which in consequence of that effect is usually recommended in cases of heart disease in conjunction with the measures already deprecated. In inadequacy of the aortic valves the pulse generally ranges from 90 to 110. After each contraction of the ventricle during the pause or interval of rest occurring between that contraction and the next following a quantity of blood is regurgitating into the ventricles. The

danger of the disease is in proportion to the quantity of blood that regurgitates, and the quantity that regurgitates will be large in proportion to the degree of inadequacy of the valves and to the length of the pause between the contractions of the ventricle during which the blood can be pouring back. If the action of the heart be rendered very slow, the pause after each contraction will be long, and consequently the regurgitation of blood must be considerable. Frequent action of the heart, on the contrary, makes the pause after each contraction short, and in proportion as the pauses are shortened the regurgitation must be lessened. Instead, then, of regarding an increase of frequency in the action of the heart as an aggravation of the disease, it must be viewed, as we have already viewed hypertrophy of the heart, as a provision for remedying as far as possible the evil consequences arising from inadequate valves. To retard in such circumstances the action of the heart would be to do an injury. In every case of this disease in which digitalis has been administered it has invariably aggravated the patient's sufferings. The oppression has become greater, the action of the heart more labored, the pulse intermittent and very often dicrotic from the heart's being unable by a single contraction to empty itself; general congestion and dropsy if present have been increased, and in some instances bronchitis from congestion has been induced; the respiration became laborious, and the strength so much sunk that patients seemed almost moribund. From this state they only recovered by omitting the digitalis and being placed on stimulants. In no case of this disease did digitalis produce the slightest good effect, and in all, the patients while under its exhibition were always worse.

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Although the cure of inadequacy of the aortic valves is out of the reach of medicine, a correct knowledge of the nature of the affection is not the less necessary. The patient is relieved from harrassing treatment, that, however applicable in other cases of heart disease, is not alone useless but positively injurious in this. In other affections of the heart there is a constant danger of sudden death from pulmonary apoplexy or hemorrhage, which may be induced even by ordinary exertion, and such danger keeps the patient in a state of perpetual terror. In this disease, on the contrary, assurance may be given against any sudden termination, and the patient may be permitted not only to attend to his business or profession but may be assured that, in leading a life of business and tolerable activity, he is adopting the very best means of prolonging life. Under treatment such as recommended, it is astonishing what little uneasiness inadequacy of the aortic valves will produce—indeed, very often not so much as those organic affections or growths of the liver, which are nevertheless viewed by the profession and by patients with much less terror.

Explanation of Plate

Fig. 1.—Reticulated valves: *A, A, A, A,* openings produced by absorption in valves, through which blood regurgitated; these valves were slightly thickened.

Fig. 2.—*A,* left hand valve, with opening through it large enough to admit goose quill, and ruptured from its connection with the aorta so that it flapped back into the ventricle; *B,* bony depositions on inner coat of aorta; *C,* middle and right hand valves thickened and contracted in their free edges, so that they could be separated only a short distance from sides of aorta.

Fig. 3.—*A, A,* openings in valves, as in figure 1, produced by absorption, one of the openings in right hand valve being large enough to permit finger to pass through; *B,* middle valve, projecting downward, curled back and bound to the aorta by bony deposition, so that it was totally useless; *C,* bony deposition tying edges of middle and right hand valves together, and at same time gluing them to aorta.

Fig. 1.

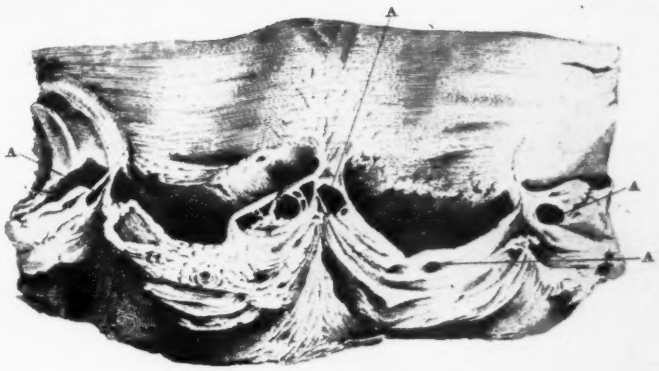


Fig. 2.

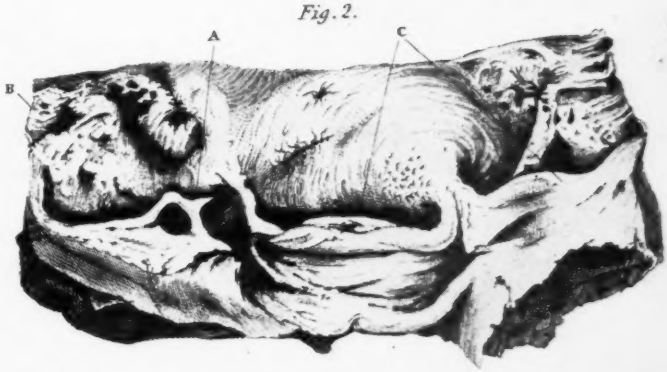
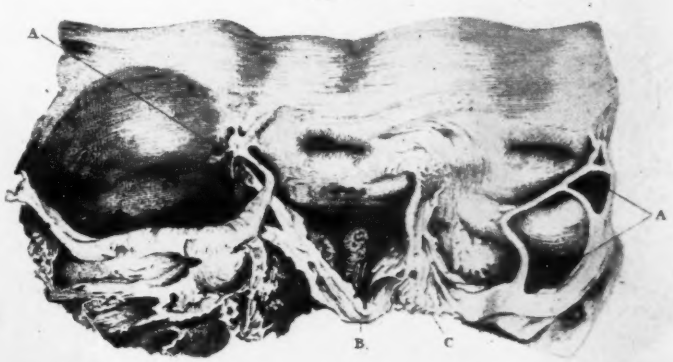


Fig. 3.



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A CONFIRMATORY SIGN OF FREE FLUID IN THE PLEURAL SPACE

PRELIMINARY REPORT *

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The positive diagnosis of free fluid in the pleural space is difficult in some cases. Clinical observations on a series of patients seen during the last two and a half years have convinced me that the physical signs elicited high in the axilla of the affected side give information of value in the differentiation between free fluid and other conditions that may simulate it. In this series it was noticed that fluid was obtained on puncture in those cases showing the usual physical signs provided these signs were accompanied by dulness on percussion and a decrease in the intensity of the breath sounds high in the axilla of the affected side.

One group of cases showed signs that were taken to be those of an effusion. Examination high in the axilla revealed practically normal findings and on puncture no fluid was obtained. The underlying pathologic condition in this group was usually found to be a thickened pleura or an immobility of the diaphragm which so often accompanies and follows pulmonary and pleural disease.

Another group showed axillary dulness and signs in the back simulating free fluid, but the high axillary dulness was accompanied by exaggerated breath sounds. No fluid was obtained on puncture in such cases and the underlying condition was usually found to be a consolidation process.

Even slight dulness or a slight diminution in the intensity of the breath sounds is important because it was found that the amount of effusion is roughly proportional to the amount of dulness and change in the intensity of breathing high in the axilla. Slight dulness and slight diminution in breathing were observed with small effusions, while marked dulness and decided decrease in the intensity of the breath sounds were observed with large effusions. It was found important to examine *high* in the axilla and to refer and compare with the signs in "normal areas," comparison with the areas below the centers of the clavicles and with the axillary space of the opposite side being especially helpful.

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* From the department of internal medicine, hospital division of the Medical College of Virginia.

* Read before the Richmond Academy of Medicine, October, 1925.

Mouriquand [1] in 1919 discussed the importance of axillary dulness in the diagnosis of pleural effusions, but did not mention the changes in the breath sounds. These changes are of importance because, as has been stated, dulness may also be present high in the axilla with lung consolidation as well as with fluid.

Ellis' line found in moderate effusions further substantiates the axillary dulness because the summit of the S shaped curve is found in the axilla. Dulness, however, occurs in many cases high in the axilla without the other component parts of Ellis' curve and, as has been stated, with a decrease in the intensity of the breath sounds. It is this change in the breath sounds that is sometimes almost diagnostic.

Cabot [2] says that "the position of the effusion depends only in part upon the influence of gravity, and is greatly influenced by capillarity and the degree of retraction of the lungs. Consequently the surface of the fluid is hardly ever horizontal. With the patient in an upright position it usually reaches a higher level in the axilla than in the back." From this statement it would seem that in the upright position at least, the high level of the fluid in the axilla would give rise to signs of fluid in this place. This conclusion conforms with the high axillary signs that have been observed in such cases.

The following cases illustrate the practical value of physical findings high in the axillary space:

REPORT OF CASES

CASE 1.—*Pleurisy with effusion.*

Miss M. B., aged 21, a nurse, on physical examination showed diminished expansion of the left side of the chest with Litten's sign absent on this side and present on the right side. The percussion note was flat from the angle of the scapula down and impaired above this mark. In front the percussion note was flat from the third rib down. Tactile fremitus was decreased in the flat areas; whispered voice was absent in the base and breath sounds were markedly diminished. High in the left axilla the percussion note was flat and breath sounds were distant. A diagnosis of free fluid in the left pleural sac was made and 1,300 cc. of straw colored fluid removed.

CASE 2.—*Cardiac decompensation with bilateral hydrothorax.*

B. H., a white man, aged 55, admitted for failing compensation of the heart, showed but little chest expansion and was flat from the interscapular areas down on both sides. The flat areas showed decreased transmission in the intensity of the breath and voice sounds. A diagnosis of bilateral hydrothorax was made on these findings. There was dulness high in both axillae, and there also was decreased transmission of the breath and voice sounds. The next day 740 cc. of a brownish fluid was removed from the right side of the chest; fluid was still running from the needle when the aspiration was discontinued. Three days later, the signs in the left chest being the same as on admission, aspiration of this side was done and 1,600 cc. of an amber fluid removed.

1. Mouriquand, Georges: Axillary Dulness in the Diagnosis of Pleural Effusions, M. Press and Circ. **159**: No. 23 (Dec. 3) 1919.

2. Cabot, Richard C.: Physical Diagnosis, Ed. 7, New York, William Wood & Co., 1922, p. 326.

CASE 3.—*Pleurisy with effusion followed by chronic fibrous pleurisy (thick pleura).*

Mrs. L. D., a white woman, aged 19, showed the classical signs of fluid in the left base, the flatness beginning at the scapula. The signs in the axilla confirmed the diagnosis of fluid. Seven hundred and fifty cubic centimeters of straw-colored fluid was then removed. The fluid reaccumulated and six days later 750 cc. more was removed. Examination ten days later showed flatness in the base with dulness above reaching to the midscapular region. In this area tactile fremitus and whispered voice transmission decreased. These signs pointed either to more fluid or to a thick pleura in the base. A roentgen-ray report of the chest stated "it is probable that the pleural thickening contains a small amount of fluid." The percussion note was resonant high in the axilla and the breath sounds were of normal intensity. A needle was inserted into the flat area the next morning and no fluid was obtained.

CASE 4.—*Small amount of free fluid.*

T. C., a man, aged 23, was admitted acutely ill. The temperature was 101 F.; respiration, 36, and pulse, 120. The left lung showed the percussion note to be dull from the apex to the base, being almost flat in the base. The spoken voice and the breath sounds were decreased in intensity on the left from the midscapular area down. There were no râles, no rubs and no tubular breathing. The percussion note was resonant high in the axilla, and the breath sounds were well heard.

Twenty-four hours later a to-and-fro friction sound was heard on the left in the third and fourth interspaces in front. The signs in the back were the same except that the note now was definitely flat in the base. High in the left axilla the percussion note was found to be resonant but the intensity of the breath sounds decreased. The roentgenologist's report of roentgenograms taken on this day was that "appearances indicate a pneumonia involving the whole of the left lung." The clinical impression was that this was a case of lobar pneumonia with involvement of the pleura and that a small amount of fluid was present in the pleural sac. The signs in the base, however, were those of a moderate amount of free fluid. A needle was inserted in the back in the space below the angle of the scapula and only 15 cc. of straw-colored fluid was found. Recovery took place gradually; the signs in the chest cleared up entirely, and the patient was discharged one month later in good health.

CASE 5.—*Carcinomatosis with ascites and a small amount of free fluid in the pleural sac.*

J. W., a colored man, aged 31, showed a large irregular mass in the epigastrium and the general clinical picture of carcinoma of the stomach. In addition there was a marked ascites. The chest showed flatness behind on both sides, higher on the right, where it reached to the interscapular area. The bases showed a decrease in the intensity of the breathing and the transmission of the voice. These signs could either be due to fluid or to pushing up of the diaphragm by the ascites. The percussion note high in the right axilla was faintly dull, however, and the breath sounds questionably decreased in intensity. These signs pointed to a small amount of free fluid in the right pleural sac. The summit of the diaphragm on inspiration was seen by roentgenologic examination to reach the ninth rib in the scapular line. A needle was inserted into the eighth interspace and 25 cc. of an amber, slightly turbid fluid withdrawn. No more fluid was obtainable. An exploratory laparotomy done eleven days later revealed a large carcinoma of the stomach with extensive metastases and a large amount of fluid free in the abdominal cavity. Metastases were felt with the finger on the diaphragm and it is likely that there were metastases to the pleura; this would account for the fluid in the pleural sac.

CASE 6.—*Spontaneous pneumothorax.*

William T., a white man, aged 42, was admitted very cyanotic, orthopneic and prostrated. The temperature was 104 F., and the pulse, 130. There was

marked impairment of the percussion note in the entire right side of the chest; the note, however, was not definitely flat. Tactile fremitus was absent on the right and the spoken voice and the whispered voice were not heard. There were no râles and no friction sounds. On account of the fever and a white blood cell count of 20,400 cells per cm. it was thought that an empyema was present. There was no tympany in front or back. The patient had been sick for seven weeks and had been bringing up purulent sputum. High in the axilla on the right there was an impaired percussion note which was, however, tympanitic, and there were no breath sounds. A needle was inserted at the angle of the scapula; no fluid was obtained. The roentgenologist's report of roentgenograms taken later in the day stated that the "patient has a total collapse of the right side. The heart and mediastinum are displaced to the left. There appears to be a pneumonia involving the left lung." The next day the patient died.

CASE 7.—*Pneumonia.*

R. B., a colored man, aged 29, was admitted suffering with lobar pneumonia of both lobes on the left side. Two days after admission the left base was flat and the breath sounds were not heard, while above, in the interscapular area, the percussion note was dull and the breath sounds tubular. Anteriorly, in the apex, the percussion note was hyperresonant; below the third rib many crepitant râles were heard. High in the axilla the percussion note was resonant and crepitant râles were heard.

The patient had been acutely ill for nine days prior to admission; he appeared to be getting worse, and in the base of the left side of the chest there were signs of either fluid or a very thick pleura. A needle was therefore inserted in the flat area behind, but no fluid was obtained. The next day the patient died suddenly. Necropsy showed the right lung to be normal; the left was in a stage of resolution; both pleural sacs were free of fluid. The heart was markedly dilated, filled with blood and very flabby.

CONCLUSIONS

1. Dulness and decrease in the intensity of the breath sounds high in the axilla of the affected side is a confirmatory sign of free fluid in the pleural sac.

2. Dulness with an increase in the intensity of the breath sounds high in the axilla on the side that otherwise shows the classical signs of free fluid does not confirm this diagnosis, and is usually indicative of consolidation rather than of fluid.

3. This sign appears to be of value in differential diagnosis, especially between a thick pleura at the base and free fluid.

4. Interpretation of the findings high in the axilla is not puzzling, but the elicitation of the finer shades of dulness and decreased intensity of breath sounds is difficult and comparison with normal areas on the chest must be carefully made.

5. The amount of fluid present is roughly proportional to the extent and degree of dulness and of decrease in the intensity of the breath sounds high in the axilla.

6. The high level in the axilla of free fluid due to capillarity and the degree of retraction of the lungs forms the basis for the signs of fluid in the axilla.

209 Professional Building.

BILIARY SYSTEM FUNCTION TESTS*

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My object in undertaking the work discussed in this article was to evaluate the tests for biliary function that have been advocated as being of practical help to the clinician in the diagnosis or prognosis of disturbances of the biliary system.

A practical test of hepatic function must satisfy the following requirements:

1. It must give information of a quantitative nature as to the functional capacity of any one element of the biliary system or of the biliary system as a whole.

2. The technic of the test must be so simple that it can be carried out by any one familiar with laboratory methods.

3. The performance of the test must require a minimal amount of time and equipment.

The liver is a complex organ and has many functions to perform. The problem of finding any one test which throws light on all the functions of the liver or which determines the capacity of this organ to perform any one of its varied services is a difficult one. Moreover, tests used for estimating liver function may be influenced by factors outside the liver, such as obstruction of the bile ducts, changes in the circulation, and even by changes in the hemoglobin content of the blood, as this has been shown by Rous [1] to influence the excretion of bile.

A variety of different tests have been suggested for determining the functional activity of the liver and much work has been done in an effort to establish the clinical value of such tests. For example, Strauss [2] used levulose as a liver function test, while Bauer [3] suggested galactose for the same purpose. A study of the value of nitrogen partition in the blood as a functional test for the liver was first undertaken by Chesney, Marshall and Rowntree.[4] Wilbur and Addis,[5] as well as Einhorn,[6]

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* From the medical clinic of the Peter Bent Brigham Hospital.

* This paper is No. 62 of a series of studies in metabolism from the Harvard Medical School and allied hospitals. The expenses of this investigation have been defrayed in part by a grant from the Proctor Fund of the Harvard Medical School for the study of chronic disease.

1. Rous, P., and Drury, D. R.: J. Exper. Med. **41**:601 (May) 1925.
2. Strauss, L.: Deutsche med. Wchnschr. **27**:757, 1901.
3. Bauer: Wien. med. Wchnschr. **56**:20, 1906.
4. Chesney, A. M.; Marshall, E. K. Jr., and Rowntree, L. G.: J. A. M. A. **63**:1533 (Oct.) 1914.
5. Wilbur, R. F., and Addis, Thomas: Arch. Int. Med. **13**:235 (Feb.) 1914.
6. Einhorn, Max: More Practical Functional Tests of Liver, J. A. M. A. **81**:1494 (Nov.) 1923.

have made use of urobilin and urobilinogen determinations in the urine. Whipple [7] and his co-workers suggested the fibrinogen and the lipase tests for liver function, and Goodpasture [8] suggested the fibrinolytic ferment test as an aid in diagnosing the liver cirrhoses. The value of the various methods mentioned above, most of which were introduced prior to 1914, has been discussed by Rowntree, Hurwitz and Bloomfield,[9] by Krumbaar,[10] and by Chesney, Marshall and Rowntree,[4] the general conclusion being that the tests suggested have been of limited practical value.

With the exception of Widal's [11] hemoclastic crisis test and the fat droplet (hemaconia) determination of Brulé,[12] the more recent methods have been dependent either on the excretion of a dye by means of the liver or on the determination of the bilirubin content of the blood serum. The use of the dye phenoltetrachlorphthalein was suggested by Rowntree [9] in 1913. The dye was injected intravenously and the amount excreted through the liver in a unit of time was determined by quantitative studies of the feces. This test was modified by McNeil,[13] who estimated the dye present in the bile after collecting it through a duodenal tube. Rosenthal [14] further modified the method by following the retention of the dye in the blood rather than its excretion in the feces or in the bile. The use of other dye substances has been advocated more recently, e. g., rose bengal by Delprat and others,[15] azorubins by Tada and Nakashima,[16] and bromsulphalein by Rosenthal and

7. Whipple, G. H., and Hurwitz, S. H.: J. Exper. Med. **13**:136, 1911. Whipple, G. H.; Mason, V. R., and Peightal, T. C.: Bull. Johns Hopkins Hosp. **24**: 207, 1913. Whipple, G. H.; Peightal, T. C., and Clark, A. H.: Bull. Johns Hopkins Hosp. **24**:343, 1913. Whipple, G. H.: Am. J. Physiol. **33**:50, 1914.

8. Goodpasture, E. W.: Bull. Johns Hopkins Hosp. **25**:330, 1914.

9. Rowntree, L. G.; Hurwitz, S. H., and Bloomfield, A. L.: Bull. Johns Hopkins Hosp. **24**:327, 1913.

10. Krumbaar, E. B.: New York M. J. **100**:719 (Oct.) 1914.

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12. Brulé: Les recherches récentes sur les ictères, 1919.

13. McNeil, H. L.: J. Lab. & Clin. Med. **1**:822, 1916.

14. Rosenthal, S. M.: J. Pharm. & Exper. Therap. **9**:385 (June) 1922; New Method of Testing Liver Function with Phenoltetrachlorphthalein, J. A. M. A. **79**:2151 (Dec. 23) 1922; Proc. Soc. Exper. Biol. & Med. **21**:2271, 1923; Phenoltetrachlorphthalein Test for Hepatic Function: Recent Studies with the Author's Method, J. A. M. A. **83**:1049 (Oct. 4) 1924.

15. Delprat, G. D.; Epstein, N. N., and Kerr, W. J.: New Liver Function Test; Elimination of Rose Bengal When Injected into Circulation of Living Subjects, Arch. Int. Med. **34**:533 (Oct.) 1924.

16. Tada, Y., and Nakashima, K.: New Dye for Test of Liver and Biliary Tract Function, with Especial Reference to Its Clinical Use, J. A. M. A. **83**:1292 (Oct. 25) 1924.

White.[17] Graham and Cole [18] introduced a method of visualizing the gallbladder by means of the roentgen rays after the intravenous injection of an opaque medium. Several dyes, opaque to the roentgen rays, were tried by these investigators, who recommended the sodium salt of tetrabromphenolphthalein. Whitaker and Milliken [19] demonstrated certain advantages of tetraiodophenolphthalein over tetrabromphenolphthalein for intravenous injection, while Whitaker, Milliken and Vogt [20] have been able to visualize the gallbladder after the oral administration of the iodo salt. Although certain toxic effects have been reported by those working with these dyes, there have been no fatalities reported and the method is being used with definite value in the diagnosis of gallbladder disease. Milliken and Whitaker [21] report correct diagnoses by the intravenous method in 95 per cent of a series of twenty proved cases of gallbladder disease, while the clinical impression was correct in only 65 per cent of the same series.

For the determination of the serum bilirubin van den Bergh and Snapper [22] made use of Ehrlich's diazo test. They found that when the diazo reagent (sulphanilic acid and sodium nitrite) was added to the blood serum of certain jaundiced patients a color reaction resulted, while in other cases the color was produced only after the addition of alcohol. Van den Bergh designated these reactions, respectively, the "direct" and the "indirect" reactions and believed that the "direct" reaction occurred only in cases of obstructive jaundice whereas the "indirect" reaction occurred as the result of jaundice of hemolytic origin. Lepehne,[23] McNee,[24] Andrews [25] and others have used the van den Bergh test clinically and have considered the "direct" and the "indirect" reactions to be of diagnostic value. Greene, Snell and Walters [26] question the diagnostic value of the "direct" and the

17. Rosenthal, S. M., and White, E. C.: Clinical Application of Bromsulphalein Test for Hepatic Function, J. A. M. A. **84**:1112 (April 11) 1925.

18. Graham, E. A., and Cole, W. H.: Roentgenologic Examination of Gallbladder; New Method Utilizing Intravenous Injections of Tetrabromphenolphthalein, J. A. M. A. **82**:613 (Feb. 23) 1924. Graham, E. A.; Cole, W. H., and Copher, G. H.: Visualizing of Gallbladder by the Sodium Salt of Tetrabromphenolphthalein, J. A. M. A. **82**:1777 (May 31) 1924.

19. Whitaker, L. R., and Milliken, G.: Surg. Gynec. Obst. **40**:17 (Jan.) 1925.

20. Whitaker, L. R.; Milliken, G., and Vogt, E. C.: Surg. Gynec. Obst. **40**: 847 (June) 1925.

21. Milliken, G., and Whitaker, L. R.: Surg. Gynec. Obst. **40**:646 (May) 1925.

22. Van den Bergh, A. A. H., and Snapper, J.: Deutsches Arch. f. klin. Med. **110**:540, 1913.

23. Lepehne, G.: Deutsches Arch. f. klin. Med. **135**:79 (Jan.) 1921; abstr., J. A. M. A. **76**:1051 (April 9) 1921.

24. McNee, J. W.: Quart. J. Med. **16**:390 (July) 1923.

25. Andrews, C. H.: Brit. J. Exper. Path. **5**:213 (Aug.) 1924.

26. Greene, C. H.; Snell, A. M., and Walters, W.: Diseases of Liver; Survey of Tests for Hepatic Function, Arch. Int. Med. **36**:248 (Aug.) 1925.

"indirect" reactions, but state that "enough is known of the indirect reaction as a quantitative measure of the serum bilirubin to assure its accuracy and reliability for clinical purposes." They have, however, suggested that the color quality of the standard solution and of the reaction in the unknown serum is not identical. Blankenhorn [27] in 1917 suggested dilution of the blood plasma in order to determine the presence of increase in the bilirubin content of the blood, particularly in pernicious anemia. Meulengracht,[28] also using plasma, suggested the use of an apparatus similar to the Sahli hemoglobinometer for comparison with a 1 : 10,000 potassium bichromate solution. Gram [29] used serum in the place of plasma. Maue [30] suggested the use of the Duboscq colorimeter for the color comparisons. More extensive studies as to the clinical value of this method have been made by Meulengracht [31] and by Bernheim.[32] Fouchet [33] suggested the determination of the intensity of the green color produced when the bilirubin of serum was converted into biliverdin by the addition of a dilute acid to the serum.

It is evident from the foregoing rather brief discussion of the literature that a rather considerable amount of work has been done in studying tests of biliary function. The great bulk of the more recent work has been centered on the clinical use of various dye substances in relation to biliary function and on the determination of the bilirubin content of the serum.

Two tests were selected for this work from among the various tests enumerated above: Rosenthal's [14] modification of the phenoltetrachlorphthalein test and the so-called icterus index modified from the work of Blankenhorn [27] and of Meulengracht.[28] As the results in both of these tests may be influenced by disturbances in the biliary system other than disturbances of the liver function, it would seem advisable to speak of them as biliary system function tests rather than as liver function tests.

DESCRIPTION OF METHODS USED

Phenoltetrachlorphthalein Tests.[34]—The technic as described by Rosenthal [14] was followed in the use of the phenoltetrachlorphthalein test. The test as used is:

27. Blankenhorn, M. A.: Pernicious Anemia, Arch. Int. Med. **9**:344 (March) 1917.
28. Meulengracht, E.: Deutsches Arch. f. klin. Med. **132**:285 (July) 1920.
29. Gram, H. C.: Ugesk. f. Læger **82**:1137 (Sept. 2) 1920.
30. Maue, H. P.: Surg. Gynec. Obst. **34**:752 (June) 1922.
31. Meulengracht, E.: Ugesk. f. Læger **83**:655 (May 19) 1921; Acta med. Scandinav. **53**:827 (Jan.) 1921; Ugesk. f. Læger **85**:325 (May 10) 1923.
32. Bernheim, Alice R.: Icterus Index (a Quantitative Estimation of Bilirubinemia); Aid in Diagnosis and Prognosis, J. A. M. A. **82**:291 (Jan. 26) 1924.
33. Fouchet, A.: Compt. rend. Soc. de biol. **80**:826, 1917.
34. The disodium salt of phenoltetrachlorphthalein used in this work was obtained in 2 cc. ampules from Hynson, Wescott and Dunning. Each cubic centimeter of solution contained 50 mg. of the dye.

Five milligrams of the dye for each kilogram of body weight is given intravenously with approximately 150 cc. of physiologic sodium chloride solution. This may be easily injected into one of the large veins of the arm by means of a 30 cc. syringe and three-way stop cock. Small bore tubing is connected with the stop cock so that connections are made, respectively, with a needle introduced into a vein, a flask containing physiologic sodium chloride solution, and a syringe into which the proper amount of dye has been drawn. By proper adjustments of the stop cock the dye may be diluted with the saline solution and injected into the vein. Because of the loss of dye from leakage when the all glass syringes are used it is well to use a tight fitting Record syringe. Samples of 4 or 5 cc. of blood are taken at intervals of fifteen minutes, one hour and two hours after the injection. As the dye may cling to the walls of the vein as well as to the needle or syringe, it is customary to withdraw blood from the other arm and with a different set of apparatus. The serum is then separated from the cells by centrifugalization and is removed by pipet to two 10 mm. test tubes. To one of these tubes, which should contain approximately 0.8 cc. of serum, is added 0.2 cc. of a 5 per cent sodium hydrate solution in order to produce an alkaline medium in which the purple color of the dye develops. The concentration of the dye in the alkalinized serum is then determined by comparison with permanent standards.[35] The comparison is made with the use of a simple comparator and direct daylight, using the tube of unalkalinized serum behind the tube of standard solution in order to make the medium of the alkalinized tube and the standard tube comparable. The figure obtained by such a comparison represents the amount of dye retained in the blood serum at the time of drawing the blood.

Icterus Index Test.—The color of the blood serum due to variations in its content of bilirubin may be accurately recorded by comparison of the serum with a standard. This is the so-called icterus index test. Several methods have been suggested for such a comparison. The method described by Maue,[30] and subsequently by Bernheim,[32] was used in the earlier part of the work, the technic of which is: A quantity of blood, approximately 5 cc., is withdrawn from an arm vein and is

35. Permanent standards for comparison may be prepared as described by Hogen (J. Lab. & Clin. Med. **8**:619 [June] 1923) and Smith (Am. J. Obst. & Gynec. **8**:298 [Sept.] 1924). Ten milligrams of phenoltetrachlorphthalein is added to 100 cc. of distilled water. This strength was suggested by Rosenthal as representing the approximate concentration that would be reached if all the injected dye remained in the plasma. We consider this standard as representing 100 per cent and prepare a series of standards in small uniform sized 10 mm. tubes, ranging from 2 per cent to 30 per cent on the even numbers. To each tube 1 or 2 drops of 5 per cent sodium hydroxide solution is added in order to bring out the color. The tubes are then sealed and if kept in a dark place do not change color appreciably over a period of several months.

placed in a test tube. All apparatus used should be clean and dry in order to avoid hemolysis. The blood is allowed to stand at room temperature until retraction of the clot has occurred and is then centrifugalized with as little disturbance of the blood as possible. The serum is removed by means of a pipet and compared with a 1 : 10,000 solution of potassium bichromate in the cup of a colorimeter set at 15 mm. The depth of the standard, in this case 15, divided by the reading on the serum scale represents the icterus index of the serum. In highly colored serum it is necessary to dilute with physiologic sodium chloride solution in order to make the comparison. When the dilution is necessary the figure obtained by dividing 15 by the colorimetric reading will be multiplied by the dilution figure. By this method no attempt is made to determine the actual amount of bilirubin present, but, on the assumption that the color variation of the serum is due to bilirubin, the increase or decrease of pigment is indicated by comparison with an arbitrary standard. For clinical purposes such a determination should suffice provided there is sufficient evidence to indicate that the color variations are caused by changes in the bilirubin.

Author's Method of Color Comparison.—In an attempt to simplify the test and to make it more universally available for clinical use, a method was introduced in which the color comparisons may be made without the use of the colorimeter. A series of standards are prepared with various dilutions of potassium bichromate. The dilutions are made to correspond with the colorimetric index figures as follows:

1 : 10,000 = 1	1 : 500 = 20
1 : 5,000 = 2	1 : 400 = 25
1 : 2,000 = 5	1 : 200 = 50
1 : 1,000 = 10	1 : 133 = 75
1 : 666 = 15	1 : 100 = 100

The solutions so prepared are kept in small test tubes of 10 mm. diameter. One or two cubic centimeters of the serum to be tested is pipetted into a similar test tube, which is placed between two of the standard colors in a small comparator until a proper match is obtained. Direct daylight illumination is always used. The figure corresponding to the dilution that matches the serum is the icterus index of the serum. Readings between those of the standards may be estimated.

The method described above has, in my series, proved simple to perform and in certain instances even more accurate than the colorimetric reading. Slight amounts of hemolysis or of clouding are often difficult to avoid even with the greatest care in obtaining serum. Such serum produces a color in the colorimeter that is difficult to distinguish from an increase of bilirubin. By means of the standards these changes appear quite distinct from the color changes produced by increased

bilirubin. To avoid the clouding, blood should be taken when the patient is in a fasting state, preferably of five or more hours' duration.

In case of any considerable degree of hemolysis some of the hemoglobin may be decolorized by the addition of a few drops of 3 per cent hydrochloric acid solution. An approximate reading may then be obtained. It has also been possible to extract the fat from cloudy serum with ether without an apparent alteration of the bilirubin.

TABLE 1.—*Results in Cases Tested by Intravenous Injection of Phenoltetrachlorphthalein*

Case	Icterus Index	Per Cent of Retained Dye in 15 Minutes	1 Hour	2 Hour	Palpable Liver	Jaundice	Diagnosis Confirmed by	
1	50	18	19	16	+	+	Postmortem	Cirrhosis of liver
2	40	12	13	8	+	?	..	Cirrhosis of liver
3	25	8	12	10	+	+	..	Cirrhosis of liver
4	20	8	12	8	+	+	Postmortem	Cirrhosis of liver
5	—	8	10	8	+	—	—	Cirrhosis of liver
6	18	8	6	4	+	—	Operation	Cirrhosis of liver
7	—	8	4	3	—	—	Postmortem	Cirrhosis of liver; splenomegaly
8	8	6	2	Trace	—	—	—	Cirrhosis of liver; splenomegaly
9	19	11	12	7	+	+	—	Cirrhosis of liver (?); chronic alcoholism
10	—	5	7	4	+	—	—	Cirrhosis of liver (?); gastric ulcer
11	50	10	9	5	+	+	—	Cirrhosis of liver (?); malignant disease of liver (?)
12	125	22	30	28	—	+	—	Catarrhal jaundice
13	125	20	18	14	—	+	Operation	Carcinoma of pancreas
14	56	16	14	12	?	+	—	Carcinoma of pancreas
15	50	6	10	8	+	+	—	Metastatic malignancy of liver and lung
16	75	10	12	10	—	+	—	Carcinoma of liver (?)
17	16	8	10	8	—	+	Operation	Cholelithiasis (common duct)
18	13	6	4	2	—	+	—	Cholelithiasis
19	12	7	—	Trace	—	—	Operation	Subacute appendicitis (cholelithiasis ?)
20	14	4	1	0	—	+	Operation	Hodgkin's disease
21	—	7	—	2	—	+	—	Carcinoma of pancreas; pneumonia
22	3	5	3	0	+	—	—	Carcinoma of liver (?)
23	5	4	Trace	0	—	—	Postmortem	Pellagra; cholelithiasis
24	8	7	2	Trace	—	—	—	Neurasthenia
25	6	2	Trace	0	—	—	Operation	Carcinoma of ovary
26	—	4	1	0	—	—	—	Myeloid leukemia
27	—	4	1	0	—	+	—	Pernicious anemia
28	8	5	1	0	—	—	—	Chronic nephritis
29	—	4	2	Trace	—	—	—	Chronic nephritis
30	—	4	1	0	—	—	—	Chronic nephritis
31	—	4	1	0	—	—	—	Chronic nephritis
32	—	4	2	0	—	—	—	Chronic nephritis
33	5	4	2	0	—	—	—	No disease
34-50	..	6	2	0	—	—	—	17 cases of diabetes mellitus showing maximum and minimum retention

OBSERVATIONS WITH THE PHENOLTETRACHLORPHTHALEIN TEST

The results obtained by the use of the phenoltetrachlorphthalein test in fifty cases are shown in table 1. In this series dye retention not to exceed 6 per cent in fifteen minutes, 2 per cent in one hour and a trace in two hours is considered normal. The diagnosis used is that recorded in the clinical record of the case, wherever possible confirmed by operation or at necropsy.

In eleven cases of biliary cirrhosis varying degrees of abnormal dye retention were found in all but one (case 8). In this case there was rather marked ascites with distention of the abdomen, making palpation difficult. After removal of 11 liters of ascitic fluid, the spleen was barely palpable while the liver edge could not be definitely felt. Jaundice was not present. A diagnosis of splenomegaly and biliary cirrhosis was made in this case. The clinical picture of case 7 resembled that of case 8. Rather marked ascites made palpation of the abdomen difficult. The spleen was palpable but the liver was not. Jaundice was not present. There was a history of prolonged alcoholism. A diagnosis of splenomegaly and biliary cirrhosis was made. Splenectomy was performed, at which time a biopsy confirmed the diagnosis of biliary cirrhosis, the liver being slightly enlarged. Dye retention in this case was slightly greater than in the normal group. In the other nine cirrhosis cases, there was little question as to the presence of liver disturbance. Although the phenoltetrachlorphthalein retention in these cases offered confirmatory evidence of liver disturbance, it did not aid in the differential diagnosis.

In four cases of obstructive jaundice due to other causes than cirrhosis (cases 12, 13, 14 and 17) the dye retention was high. Carcinoma of the pancreas accounted for the obstruction in two of these; one patient had catarrhal jaundice, while obstruction in the fourth case was caused by a stone in the common duct. Definite jaundice was present in all. As the other evidences of obstruction were quite definite, the test was of no diagnostic value.

In one case (case 15) in which metastasis to the lung and liver had occurred from a hypernephroma there was a moderate degree of dye retention.

Patient 16 became jaundiced ten days before admission to the hospital, at which time the liver was palpable but not nodular. Cholecystectomy had been done seven months before, with relief of symptoms at that time. The dye retention figure was moderately increased in this case.

In a case (case 18) diagnosed as having cholelithiasis, in which jaundice was present, there was no abnormal retention of dye.

In the other thirty-two cases of this series there was no evidence of abnormal dye retention. One case of pernicious anemia and seventeen cases of diabetes are included in this normal group. All these cases were well within the limits of normal dye retention. This observation does not support the findings of Piersol and Bockus,[36] who report a dye retention slightly greater than their normal figure in three of four diabetic patients tested.

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36. Piersol, G. M., and Bockus, H. L.: Comparative Studies in Liver Function by Some of the Later Methods, J. A. M. A. **83**:1043 (Oct. 4) 1924.

One other case (case 20) occurring in the normal group warrants further comment. Because of unexplained jaundice and a history suggesting gallbladder disease, an exploratory laparotomy was performed. No stones or other obstructions were found. A few weeks later enlarged glands appeared in the cervical region and a biopsy diagnosis of Hodgkin's disease was made. The negative test should perhaps have prevented the exploratory operation although the cause of the jaundice is still unexplained.

These results confirm the general impression given by the reports of several observers [37] that little information of value, either as an aid to diagnosis or prognosis, is obtained from the use of this test. On the other hand, the test has been considered by these workers and others to show rather accurately the degree of obstruction present in the cases in which an undoubted pathologic condition exists. Rosenthal [14] concludes that the figures obtained in his series "give an index of the functional capacity of the liver." Ottenberg and Rosen,[38] by retesting patients with common duct stone just prior to operation, were able to demonstrate in a few instances that the stone had been passed. The results of Rosenfield and Schneiders [39] in a series of tests on pregnant women confirm Rosenthal's conclusions. They also believe that it is of value as an index in the treatment of the toxemias of pregnancy. Smith [35] reports the test to be of value in differentiating between preeclamptic toxemia and the nephritic type in pregnancy, the retention of dye being more constant in the former. Boardman and Schoonmaker [40] concluded in part from their work on twenty-two cases of cholecystitis that "in the phenoltetrachlorphthalein test we have a valuable means of studying the functional activity of the liver." Although it has been possible to demonstrate varying degrees of liver or biliary tract dysfunction by means of the phenoltetrachlorphthalein test, little information was obtained in the series of cases reported above which was of considerable value either in the diagnosis or prognosis of the cases. It was also felt that the method was too technical and time consuming to be of practical clinical value.

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37. Ottenberg, R.; Rosenfeld, S., and Goldsmith, L.: Clinical Value of Serum Tetrachlorphthalein Test for Liver Function, Arch. Int. Med. **34**:206 (Aug.) 1924. Greene, C. H.: Minnesota Med. **8**:142 (March) 1925. Rowntree, L. G.: The Rôle of Liver Function Tests in Practice, Proc. Am. A. Phys., May, 1925; abstr., J. A. M. A. **84**:1775 (June 6) 1925.

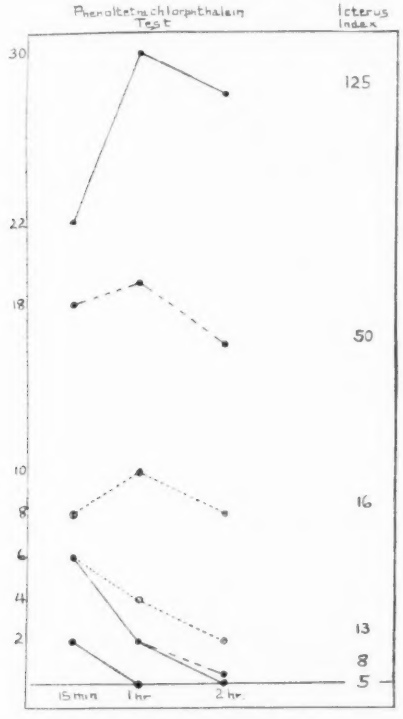
38. Ottenberg, R., and Rosen, S.: Possible Application of Phenoltetrachlorphthalein Test to Obstructive Jaundice, J. A. M. A. **80**:1519 (May 26) 1923.

39. Rosenfield, H. H., and Schneiders, E. F.: Improved Phenoltetrachlorphthalein Test for Liver Function in Pregnancy and Its Toxemias, J. A. M. A. **80**: 743 (March 17) 1923.

40. Boardman, W. W., and Schoonmaker, G. D.: Am. J. M. Sc. **168**:688 (Nov.) 1924.

OBSERVATION WITH THE ICTERUS INDEX TEST

An estimation of the icterus index was made in many of the cases discussed in the foregoing. These figures are also included in table 1, and a few are shown in the accompanying chart along with the phenoltetrachlorphthalein curve obtained in the same case. They are shown here merely to compare results of the two methods and will be included



Comparison beween phenoltetrachlorphthalein curve and icterus index in six representative cases: solid line (two lower), normals; solid line (upper), catarrhal jaundice; long dash broken line, cases of cirrhosis, and short dash broken line, cases of cholelithiasis.

in the icterus index tables. The information obtained by the use of this test in the preliminary series was quite as valuable as that obtained by the use of the more difficult and more time consuming phenoltetrachlorphthalein test. In many of these cases van den Bergh's test was also used by Evans.[41] Little information was obtained by means of this test which was not available by the use of the icterus index determination.

41. Evans, J. A.: Personal communication to the author.

Icterus index determinations made on 206 patients are recorded in this article. An index of 5 with a possible variation between 4 and 6 is considered normal.

Determinations were made on the serum of fifty-five patients without clinical signs of biliary system disease and in whom a normal index might be expected. The results are shown in table 2. Three indexes of this group were abnormal. One case of syphilis under treatment gave a reading of 8. As this patient was receiving intravenous arsenic at the time, there may have been slight liver damage although jaundice did not develop. In two instances the index was low, although there was not recorded any evidence of secondary anemia in the routine blood report of the ward.

In table 3 are shown the results of determinations made in forty cases of pernicious anemia. The index in these cases ranged from 5 up to 40.

TABLE 2.—*Miscellaneous Group of Cases in All of Which a Normal Index Might be Expected*

Diagnosis	Number of Cases	Icterus Index
No disease	15	5
Syphilis	17	5
Syphilis	1	8
Syphilis	1	2
Nephritis (chronic)	3	5
Lymphosarcoma	2	5
Obesity	3	5
Osteomyelitis	1	5
Osteomyelitis	1	4
Acute infection	1	4
Carcinoma of ovary	1	6
Polycythemia	1	5
Purpura haemorrhagica	2	5
Pancreatitis	1	5
Intestinal indigestion	1	5
Hemiplegia	1	5
Hypertension	1	5
Endocervicitis	1	5
Multiple sclerosis	1	3
Total	55	

In thirty-five of the forty cases the index was above normal (50 per cent of these ranged between 10 and 20), while in five of the forty cases the index was normal. In these cases, although the blood changes were slight, a typical history, an absence of free hydrochloric acid in the gastric contents of three patients and in all characteristic neurologic changes justified the diagnosis. These five patients were all over 40 years of age at the time of onset of symptoms and in only one case (case 36) was the duration of symptoms longer than one and one-half years. The hemoglobin reading was above 70 per cent and the red cell count was above 3,000,000 in each case. These five patients (cases 36, 37, 38, 39 and 40) all had marked neurologic changes, which accounts for the fact that they came under observation during a remission. The other thirty-five were under observation because of symptoms directly referable to the anemia. Five cases (cases 6, 7, 27, 28 and 34) of the

series, in which a high index reading was obtained when the blood count was low, were kept under observation until the count became more nearly normal, at which time the index was recorded as normal in four cases and slightly below normal in the fifth. In all, then, ten cases of pernicious anemia tested during a remission gave a normal icterus index figure. These results confirm the reports of several others who have studied the serum color in pernicious anemia. Blankenhorn [27] reported twenty cases of pernicious anemia in which the Gmelin test for bile pigment was positive in sixteen. He concluded from his series that the cases with the highest bilirubin gave the most marked evidence of rapid blood destruction, as indicated by a high color index and loss of strength. Gram [29] concluded that the bilirubin rises as the patient gets worse in pernicious anemia. Maue [30] found only one case of pernicious anemia with an increased icterus index although he does not state how many

TABLE 3.—*Determinations in Forty Cases of Pernicious Anemia*

Case	Icterus Index	Diagnosis	Case	Icterus Index	Diagnosis
1	40	Pernicious anemia	21	10	Pernicious anemia
2	35	Pernicious anemia	22	10	Pernicious anemia
3	35	Pernicious anemia	23	10	Pernicious anemia
4	30	Pernicious anemia	24	10	Pernicious anemia
5	30	Pernicious anemia	25	10	Pernicious anemia
6	30	Pernicious anemia	26	10	Pernicious anemia
7	25	Pernicious anemia	27	10	Pernicious anemia
8	25	Pernicious anemia	28	10	Pernicious anemia
9	25	Pernicious anemia	29	10	Pernicious anemia
10	25	Pernicious anemia	30	9	Pernicious anemia (combined sclerosis)
11	25	Pernicious anemia	31	9	Pernicious anemia
12	20	Pernicious anemia	32	9	Pernicious anemia
13	20	Pernicious anemia	33	9	Pernicious anemia
14	15	Pernicious anemia	34	8	Pernicious anemia
15	15	Pernicious anemia	35	7	Pernicious anemia
16	15	Pernicious anemia	36	5	Pernicious anemia (combined sclerosis)
17	15	Pernicious anemia	37	5	Pernicious anemia (combined sclerosis)
18	15	Pernicious anemia	38	5	Pernicious anemia (combined sclerosis)
19	12	Pernicious anemia	39	5	Pernicious anemia (cambined sclerosis)
20	12	Pernicious anemia	40	5	Pernicious anemia (combined sclerosis)

were tested. Bernheim [32] reported ten cases with indexes ranging from 6.5 to 12.5. The serum in which the index figure was 6.5 was taken during a remission. These various observations suggest, as might be expected, that during periods when blood destruction is going on the bilirubin content of the serum rises, while during a remission the serum color approaches normal.

Thirty-four cases showing evidence of secondary anemia are recorded in table 4. In all but six of these cases the icterus index was 4 or lower. The index determinations in these cases did not parallel either the hemoglobin or the red cell count. In several instances, however, the index became normal as the red cell count increased during convalescence following an acute fever, as occurred, for example, in case 7.

It is of interest to compare the figures in the last three tables (tables 2, 3 and 4) which suggest the value of the index test in the diag-

nosis of anemia. Of the normal group forty-three, or 78 per cent, had indexes of 5, while only three, or 5.6 per cent, had indexes that were above or below the possible normal variation of 4 to 6. In the anemia tables, although a few cases showed indexes running into the normal range, for the most part the range for the primary anemias was above normal while the secondary was below normal. Of the forty primary anemias thirty-five, or 87.5 per cent, showed an increased index, while of the thirty-four secondary anemias twenty-eight, or 82 per cent,

TABLE 4.—*Determinations in Thirty-Four Cases Showing Evidence of Secondary Anemia*

Case	Diagnosis	Sex*	Per Cent Hemoglobin	Red Cell Count	Icterus Index
1	Syphilis (secondary)	♂	80	5.0	3
2	Syphilis (secondary)	♂	75	4.5	3
3	Syphilis; duodenal ulcer	♂	80	4.5	2
4	Bronchopneumonia	♂	70	4.4	2
5	Syphilis	♂	65	4.3	3
6	Cause unknown	♀	75	4.2	5
7	Paratyphoid B fever	♂	70	4.2	2
8	Debility	♀	44	4.2	4
9	Syphilis; duodenal ulcer	♂	70	4.0	2
10	Cause unknown	♂	60	4.0	5
11	Debility	♀	60	4.0	5
12	Syphilis; duodenal ulcer	♂	70	3.7	4
13	Syphilis (secondary)	♀	63	3.7	3
14	Carcinoma of rectum	♀	60	3.6	3
15	Renal calculus (hemorrhage)	♂	56	3.6	1
16	Carcinoma of liver (metastatic)	♀	50	3.6	3
17	Endocarditis (rheumatic)	♀	70	3.5	1.5
18	Acute infection	♀	56	3.5	4
19	Cause unknown	♀	55	3.5	3
20	Banti's disease (?)	♂	40	3.5	2
21	Lymphosarcoma; syphilis	♂	56	3.4	2
22	Chronic hemorrhage	♀	50	3.2	3
23	Carcinoma of stomach	♂	45	3.0	5
24	Lymphosarcoma	♂	40	2.9	3
25	Carcinoma of stomach	♂	50	2.8	2
26	Hypernephroma	♂	50	2.6	2
27	Carcinoma of intestine	♀	40	2.5	2
28	Splenic anemia	♀	25	2.4	3
29	Duodenal ulcer (hemorrhage)	♂	40	2.3	3
30	Leukemia (atypical)	♂	41	2.0	5
31	Myeloid leukemia; aleukemia	♂	25	2.0	3
32	Splenic anemia	♂	24	1.7	5
33	Purpura haemorrhagica (hemorrhage)	♀	30	1.3	3
34	Aplastic anemia	♀	26	1.1	3

In this table thirty-four cases are recorded in which the blood count or the blood morphology indicated a secondary anemia. The red cell counts are shown by figures representing millions per cubic millimeter. The cases are arranged in order according to the red cell count, starting with the highest count.

* In this and the following tables ♂ indicates male, ♀ female.

showed a decreased pigment content. Approximately 15 per cent of the cases of both types of anemia fall into the group of those which do not show the characteristic index figures. It will be necessary in this group to anticipate the diagnosis by means of the somewhat characteristic findings in each type. These are, however, in many cases not entirely definite. The presence of free hydrochloric acid in the gastric content has been shown by Levine [42] to be a constant aid in ruling out a primary

42. Levine, S. A., and Ladd, W. S.: Bull. Johns Hopkins Hosp. **32**:254 (Aug.) 1921.

anemia. The absence of the acid, on the other hand, does not prove the presence of primary anemia.

The next series of cases include the patients in whom there was a question of a pathologic condition of the gallbladder or bile duct. As a matter of convenience in discussing this series, the cases have been divided into four groups as follows:

Group 1. This group includes four cases in which the gallbladder has been removed with subsequent attacks of pain in the right upper quadrant. The cases are shown in table 5.

In case 1 the complaint of a severe attack of right upper quadrant pain in the absence of demonstrable jaundice was at first considered an hysterical manifestation as the patient was considered to be of a neurotic temperament. She became quite definitely jaundiced during the morning after a high icterus index had been demonstrated. Three days later the icterus index was lower but still well above normal. At operation a common duct stone was removed.

Patient 2 left the hospital without operative investigation of the common duct because of lack of proof of obstruction. The index at

TABLE 5.—*Cases in Which Common Duct Obstruction Was Suspected After Cholecystectomy*

Case	Icterus Index	Sex	Age	
1	40, 25	♀	30	Common duct stone at second operation
2	17	♀	50	Adhesions; recent stone at second operation (?)
3	25	♀	65	Common duct stone (?); no second operation
4	4	♀	27	No recurrence of pathologic condition

this time was 17. Following a subsequent attack of pain with jaundice an exploratory operation was done in another hospital. The operator found many adhesions about the common duct and felt that there was evidence that a stone had recently been passed.

Patient 3 entered the hospital following an attack of pain with jaundice nine years after removal of the gallbladder. The icterus index was 25 at this time. Because of the rather convincing evidence of obstruction, operation was advised but the patient refused to have this done. Three months after leaving the hospital this patient reported that there had been no further attacks of pain or jaundice. This would suggest that if a stone were present it was passed just before her admission to the hospital.

Patient 4 had her gallbladder removed but has since complained a great deal of distress in the right upper quadrant. The index was not above normal and the patient has since begun to feel better.

Group 2. This group (table 6) includes ten cases in which a pathologic condition of the gallbladder or bile duct was demonstrated. The first six patients had a high index and at operation definite disease

was demonstrated. The sixth patient had had no recent attacks of pain and on admission had a normal index. During the next few days she had attacks of pain and the index then was 15. At operation no stones were found but there was an inflammatory reaction suggesting that a stone had recently been present in the common duct, probably recently passed. In the next three cases there had been no recent attacks of pain and the index was normal. Stones were found in the gallbladder at operation in each case. In the last case there had been no history of gallbladder disturbance. Gallstones were demonstrated at necropsy.

TABLE 6.—*Cases in Which Disease of the Gallbladder or Bile Ducts was Demonstrated at Operation or at Necropsy*

Case	Icterus Index	Sex	Age	Diagnosis Made by: Operation*	Roentgen Ray	History	Diagnosis
1	75	♀	59	+	0	+	Common duct stone
2	35	♂	38	+	+	+	Common duct stone
3	30	♂	32	+	—	+	Pericholecystitis
4	16	♀	42	+	—	+	Cholelithiasis
5	10	♀	?	+	0	+	Cholelithiasis
6	15	♀	40	+	0	+	Common duct stone (?)
7	6	♀	66	+	+	+	Cholelithiasis
8	5	♀	50	+	—	+	Cholelithiasis
9	5	♀	36	+	0	+	Cholelithiasis
10	5	♀	60	+	0	—	Cholelithiasis

* In this table, + means positive diagnosis; —, negative diagnosis, and 0, observation not made.

TABLE 7.—*Cases Suspected of Having Gallbladder or Bile Duct Disease But Not Proved*

Case	Icterus Index	Sex	Age	Diagnosis Made by: Operation	Roentgen Ray	History	Diagnosis
1	25	♀	34	0	—	+	Cholelithiasis
2	13	♀	40	0	—	+	Cholelithiasis
3	10	♂	39	0	—	+	Cholelithiasis
4	25	♀	56	0	0	+	Cholelithiasis
5	30	♀	52	0	?	+	Cholelithiasis (?)
6	18	♀	27	0	0	+	Cholelithiasis (?)
7	25	♂	32	0	—	+	No diagnosis
8	15	♂	40	0	—	+	No diagnosis
9	15	♂	40	?	—	+	Duodenal ulcer (large liver)
10	13	♀	28	0	—	+	Cholelithiasis (?)
11	12	♀	16	?—	—	?	Subacute appendicitis

There was roentgen-ray evidence of gallbladder disease in three of five cases so examined.

Group 3. In this group of eleven cases (table 7) the index was high in all. The first four had suggestive histories of cholelithiasis although roentgen-ray examination failed to demonstrate disease in the three cases so studied. In the other seven cases of the group, no satisfactory diagnosis could be made from the evidence at hand. Patient 6 was admitted to the hospital complaining of severe right upper quadrant pain occurring at intervals during a period of several weeks. There was a slight degree of jaundice present on admission. No severe pain

occurred during eighteen days under observation. During this time the index, which was high on admission, dropped to normal. Was this a case of catarrhal jaundice, with pain exaggerated by a neurasthenic person, or was the jaundice due to stone obstruction? In cases 7 and 8 no diagnosis was made although, especially in case 8, there was suggestive evidence of bile duct disease. A duodenal ulcer was demonstrated in case 9. At operation the liver was found to be enlarged, possibly owing to duct obstruction from pressure. Patient 11 had a "subacute" appendix removed but no mention was made in the operator's note as to the condition of the gallbladder or bile ducts. In five of the last seven cases of this group in which roentgenograms were taken no pathologic condition was recorded in the gallbladder region.

Group 4. In table 8 seven cases are shown in which gallbladder disease was seriously considered in the differential diagnosis, but was quite definitely ruled out. The index was normal in each case with the possible exception of case 1.

TABLE 8.—*Cases Studied as Being Possible Gallbladder or Bile Duct Diseases*

Case	Icterus Index	Sex	Age	Diagnosis Made by: Operation	Roentgen Ray	History	Diagnosis
1	7	♀	?	0	—	?	Chronic indigestion
2	6	♀	30	0	—	?	Obesity
3	5	♀	33	0	—	?	Duodenal ulcer
4	5	♀	45	0	—	?	Duodenal ulcer
5	5	♀	52	0	0	?	No diagnosis
6	5	♂	65	0	—	?	Angina pectoris (?)
7	5	♀	26	0	—	?	Gastric ulcer (?)

A series of tests on a miscellaneous group of cases is shown in table 9. The figures shown here suggest a few interesting features of the icterus index test.

1. In general the higher figures were recorded in the cases having bile duct obstruction rather than liver damage, e. g., carcinoma of the pancreas and catarrhal jaundice.

2. Cases of chronic myocarditis with passive congestion of the liver show an index higher than normal. The presence of jaundice in most of these cases was questionable clinically and not in proportion to the icterus index figure.

3. The icterus index is an accurate and easy method of following the progress of cases with jaundice. This is especially true in the cases of catarrhal jaundice.

There is no reason to discuss these cases individually as the facts of importance are shown in the table. In the first two cases of carcinoma of the pancreas artificial drainage of the bile duct was accomplished after the first icterus index determination in each case.

TABLE 9.—*Icterus Index Determinations in Several Types of Biliary System Dysfunction*

Period Between Tests*	Icterus Index	Diagnosis
9 days	{100} {50}	Cirrhosis of liver
	86	Cirrhosis of liver
4 days	{57} {19}	Cirrhosis of liver
	50	Cirrhosis of liver
13 days	[50]	
7 days	{25}	Cirrhosis of liver
	[50]	
	50	Cirrhosis of liver (?)
	50	Cirrhosis of liver (?)
	45	Cirrhosis of liver
	45	Cirrhosis of liver
33 days	{20} {40}	Cirrhosis of liver (?)
60 days	{30} {30}	Cirrhosis of liver
	18	Cirrhosis of liver (?)
30 days	[17]	
28 days	{ 8}	Cirrhosis; splenomegaly
	[8]	
	15	Cirrhosis of liver (?)
	8	Cirrhosis of liver
	5	Cirrhosis; splenomegaly
	5	Cirrhosis of liver (?)
	110	Acute yellow atrophy
	50	Malignant disease of liver
	50	Malignant disease of liver
	40	Malignant disease of liver
	12	Malignant disease of liver
	125	Catarrhal jaundice
12 days	{125} {75}	Catarrhal jaundice
2 days	[64]	
3 days	{40}	Catarrhal jaundice
	[25]	
4 days	[50]	
7 days	{30}	Catarrhal jaundice
	[15]	
	45	Catarrhal jaundice
	30	Catarrhal jaundice
	25	Catarrhal jaundice
	8	Catarrhal jaundice
10 days	[125]	
3 days	{90}	
10 days	{ 57}	Carcinoma of pancreas
	[30]	
22 days	{100} {30}	Carcinoma of pancreas
	80	Carcinoma of pancreas
	75	Carcinoma of pancreas (?)
	56	Carcinoma of pancreas (?)
	50	Chronic myocarditis
	30	Chronic myocarditis
	20	Chronic myocarditis
	20	Chronic myocarditis
	15	Chronic myocarditis
	14	Chronic myocarditis
	10	Chronic myocarditis
	5	Chronic myocarditis
	5	Chronic myocarditis
	5	Chronic myocarditis
	5	Chronic myocarditis

* Period in days between determinations.

CONCLUSIONS

1. Although the phenoltetrachlorphthalein test as modified by Rosenthal will give accurate information as to the amount of biliary system dysfunction where this is definite, it is not of practical value as a diagnostic aid, except possibly in relation to the complications of pregnancy. Information of equal or greater value may be obtained by means of the much simpler icterus index test.

2. The icterus index is of definite diagnostic value in distinguishing between the primary and the secondary types of anemia. The normal variation of the index is from 4 to 6. Figures above or below this should be considered abnormal.

3. Information of value may be obtained in cases in which obstruction of bile ducts occurs. If the obstruction is transient, blood for the test should be obtained within from twelve to twenty-four hours after the possible obstruction has occurred. In the absence of anemia, liver damage or duct obstruction, the index should be normal. There is no

reason to expect an increase of bilirubin in the serum because of the presence of stones in the gallbladder.

4. Determination of the icterus index by the method suggested gives an accurate but easy method of following the progress of a jaundiced patient.

5. The icterus index test is a test of considerable practical value to the clinician. The information obtained is of quantitative value and is easily obtained with little technical skill, expenditure of time and apparatus.

WATER METABOLISM

III. DEHYDRATION FEVERS *

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The production of high fevers in animals by dehydration has been the subject of much discussion and the literature is full of reports of exceedingly contradictory results. While our knowledge of the behavior of dehydrated infants (inanition fevers), reinforced by reports of exceedingly high temperatures produced by this means in animals, leaves no doubt that the loss of the water reserve of the body is an exceedingly important factor in temperature control, these fevers have followed no regular rule. Their artificial production is uncertain and inexplicable on the basis of dehydration alone, and so many discrepancies have occurred that many observers have denied the existance of such fevers altogether, attributing the fevers that do occur to some uncontrolled factors in these experiments. The three most commonly mentioned factors are: (1) impurities in the glucose used for dehydrating the animal (dextrins, acid elements, etc.); (2) free hydrochloric acid in the physiologic sodium chloride solution, and (3) impurities from the rubber tubing.

These studies originally undertaken to solve this problem have yielded definite results, which enable us not only to predict in advance the amount of dehydration which will take place under given stimuli, but also roughly when and how much of a rise in temperature will occur.

At the onset of the experiments it was evident that the factors mentioned above could be ruled out. Careful analysis of the dehydrating solutions used (dextrose and sodium chloride) showed no impurities, and repeated hydrogen ion estimations ruled out the acid factor. As an additional precaution huge batches of the reagents were made up each in a single large container, which lasted through the entire series of experiments. The tubing was washed for days in running water, and not changed during the series. In spite of these precautions, extreme variations in the temperature reactions occurred. In one experiment a rise in temperature to 120 would occur, and in the next no rise or but a slight one of 1 or 2 degrees. No connection between the degree of dehydration and the fever could be demonstrated. High fevers occurred in dogs which dehydrated freely and those which did not; also, slight rises took place in both classes.

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* From the department of surgery, University of Illinois College of Medicine.
* Read before the Institute of Medicine, Chicago, Feb. 27, 1926.

Studies of the amount of sugar or salt excreted and of the concentration of each in the blood also yielded negative results, and it was felt that metabolic factors could be eliminated as the dogs had no albumin or casts in the urine before the dehydration began and the blood chemistry appeared normal (p_H, urea, total nitrogen, creatinine and cholesterol).

In all this work we had overlooked the crucial point, that a dog's temperature is controlled by the evaporation of water from his tongue, as he has no sweat glands, and loses heat through the skin only by

TABLE 1.—*Experiment 44*

Female dog, weighing 12 Kg., injected intravenously with 5 per cent sodium chloride at rate of 25 cc. per kilogram per hour for ninety minutes.

Time	Intake	Output	Loss	Loss per Kg.	Albumin	Temperature
11:00	Injection begun		...	..	..	100.8
11:15	75	10	...	..	0	100.8
11:30	150	30	...	..	0	100.8
11:45	225	100	...	..	0	100.8
12:00	300	180	...	..	0	.....
12:15	375	275	...	..	0	101.4
12:30	450	385	...	..	0	101.8
12:45	450	460	10	1	Trace	102.6
1:00	450	610	160	12	+	103.0
1:15	450	665	215	18	++	103.5
1:30	450	720	270	22.5	+++	104.0
1:45 urine ceased	450	740	290	24	Clotted on heating	105.0

TABLE 2.—*Experiment 35*

Female dog, weighing 10 Kg., injected with 5 per cent sodium chloride at rate of 25 cc. per kilogram per hour for ninety minutes; mouth tied shut.

Time	Intake	Output	Loss	Loss per Kg.	Temperature
10:25	Injection begun	...	..	..	99.0
10:40	65	20	..	..	99.0
10:55	135	100	..	..	.....
11:10	190	160	..	..	99.8
11:25	260	220	..	..	100.2
11:40	320	300	..	..	101.5
11:55	375	400	25	2.5	102.8
12:15	375	435	60	6	104.0
12:30	375	475	100	10	110.0
1:00	375	520	145	14.5	110.0*
1:30†	375	530	155	15.5	110.0*
2:00	...	...	..	..	116.0

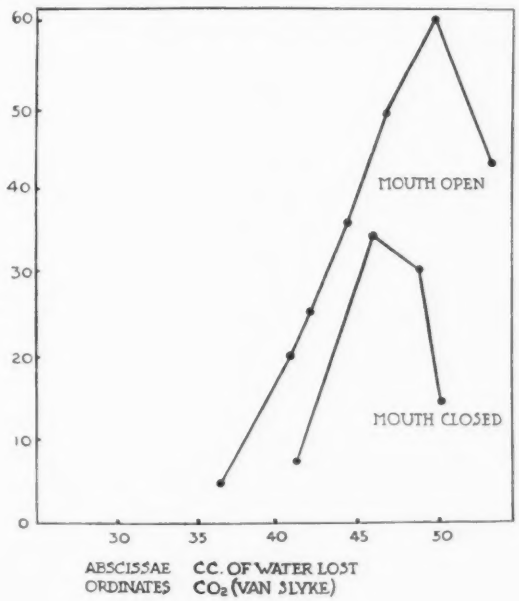
* Thermometer would not read above 110.
† Urine ceased.

radiation. Therefore, the question of the ability of the dog to ventilate his tongue is a decisive factor. As dogs lie strapped to an operating table for these experiments, some will keep the mouth open and some closed, depending on whether the head hangs over the end of the frame. If the dog's mouth is allowed to stay open he can keep his body at fairly near normal temperature (101-105) even when extreme dehydration has been brought about, as illustrated by experiment 44.

On the contrary if the dog's mouth is tied shut so that cooling off by the tongue is prevented, a more rapid rise in temperature takes place,

and in addition there is an extreme terminal rise of from 10 to 12 degrees (experiment 35).

Now in the whole series of experiments, the course of the rise in temperature is similar. In the moderate degrees of dehydration there is a slight rise (from 1 to 2 degrees) and as the limit of dehydration approaches, this increases to from 2 to 4 degrees. In no case were high fevers observed except as a terminal phenomenon. It can be shown that excretion of urine stops after the temperature has risen to 103-105. Albuminuria begins at 102 and at 105 is extreme and the flow ceases (experiment 44).



The course of any given experiment will then run as follows: The degree of dehydration possible can be predicted from the carbon dioxide, as shown in papers 1 and 2 of this series. This is true only if the dog is able to ventilate his tongue. During such an experiment the temperature will rise slowly from 2 to 4 degrees, at which point dehydration ceases and a terminal rise of 2 or 3 degrees more is likely. If the dog's mouth is tied shut at this period a terminal rise of from 10 to 12 degrees will occur. If, however, the dog's mouth is tied shut at the beginning of the experiment, the rise will be slightly more rapid and the failure of kidney function occurs a little sooner and the critical point (103-105) and extremes of temperature (116-120) are reached during the terminal stages.

It is clear that in a series of dogs with the mouth tied shut, the excretion would be less for any given carbon dioxide level. The accompanying chart shows the difference in the degree of dehydration possible in dogs with the mouth left open and with the mouth tied shut.

CONCLUSION

The unanimity of the pediatric literature in the belief in dehydration fevers is thus clear. Only the lower grades of temperature are there encountered; these, as I have shown, are always present in dehydrated animals. The experimental work done previously has given widely varying results which are due to fluctuations in the carbon dioxide, as shown in a previous article, and the presence or absence of a terminal extreme hyperpyrexia in these conflicting results can probably be attributed to the factor of the ventilation of the tongue.

A METHOD FOR THE CONTINUOUS QUANTITATIVE ESTIMATION OF GASTRIC SECRETION AND DISCHARGE IN MAN*

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The study of the pathologic physiology of the stomach has been hampered by lack of detailed knowledge of the normal motor and secretory activities of this organ. Animal experiments along the lines suggested by the ingenious work of Haidenhain and of Pawlow and their followers have, to be sure, laid down certain fundamental principles, but the results of the work can hardly be assumed to hold, as regards details, in man. Studies on human beings are to be found mainly in the literature of gastro-enterology and they have concerned themselves largely with the analysis of gastric contents following the ingestion of test meals of various sorts; their purpose has been to differentiate, if possible, various types of digestive disturbances and to lay down diagnostic criteria. Carlson and his associates have made important contributions to normal gastric physiology, without, however, investigating the wide variety of material that confronts the clinician.

Apparently no simple method is available at present for testing with reasonable completeness the secretory and motor response of the human stomach following a standard stimulus; the deficiencies of the familiar test meals may best be brought out by outlining the information that is necessary in order to have a satisfactory picture of gastric activity. In brief, an adequate test should possess the following qualifications:

1. The stimulus should be standardizable so that it may be applied repeatedly without being subject to variation.

2. The possibility, which always exists when a meal is ingested, of psychic stimulation or inhibition should be eliminated.

3. The admixture of saliva with the gastric contents should be avoided.

4. The regurgitation of duodenal contents must be controlled.

5. The procedure should yield a juice that is suitable for accurate chemical analysis.

6. One should obtain quantitative information about the fasting gastric secretion.

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7. One should obtain information about the total quantity of juice secreted during a given period as well as the hydrogen ion concentration and the total amount of acid.

8. One should obtain information about the total volume of stomach contents at various intervals after the stimulation of secretion.

9. One should obtain information about the amount of stomach contents which is discharged through the pylorus during various periods after stimulation.

10. The material obtained from the stomach should be suitable for the titration of ferments.

We have devised a simple procedure that seems to possess the foregoing qualifications. This article deals with a description of the method and with a summary of the types of information to be derived therefrom.

METHODS

In every case the subject was examined while lying quietly in bed under what may be spoken of as basal conditions. The test was started at 2 p. m. and the only nourishment taken after the evening meal on the previous day was a cup of coffee at 6 a. m. No water was allowed for four hours preceding the examination. A duodenal tube was passed for a distance sufficient to let the tip reach the most dependent part of the stomach. The tube was then strapped to the subject's chin with adhesive tape and he was furnished with a basin into which all saliva secreted during the test was expectorated. The subject was made comfortable in a semireclining position. Immediately after the passage of the tube the fasting juice was aspirated. Suction was applied with the subject on his back and after he had turned on the right and on the left sides. This maneuver was repeated on all subsequent aspirations to be sure that the stomach was completely emptied. Five minutes after the first aspiration the fasting secretion was again aspirated. If bile was present, as occasionally happened, the aspirations were repeated at five minute intervals until clear juice was obtained or until the stomach remained empty. At this point and without attracting the subject's attention 50 cc. of 7 per cent alcohol solution to which had been added 0.5 cc. of 1 per cent phenolphthalein was injected through the tube. Within one to five minutes after the injection of this alcohol meal the gastric contents were completely withdrawn into a large graduated glass syringe, the total volume was noted, and the material was immediately reinjected with the exception of 10 cc., which was retained for analysis. As a rule the specimens were colorless and limpid and barring a few particles of mucus had the appearance of clear water. Ten minutes after the previous aspiration the contents were again completely withdrawn, measured, and reinjected with the

exception of 10 cc., which again was kept for analysis. The procedure was repeated at ten minute intervals until the stomach was empty. If more than 10 cc. was present at the end of from sixty to seventy minutes the total contents were withdrawn and the test was terminated. The patients in no case complained of any discomfort due to the examination.

The fasting specimens and the samples retained from the subsequent aspirations were collected in paraffined graduated centrifuge tubes and the following examinations were made:

1. The amount and gross appearance of all the specimens were recorded.

2. In certain instances microscopic examination of centrifugated sediments was made.

3. The titratable acidity was estimated in terms of the number of cubic centimeters of tenth normal sodium hydroxid necessary to neutralize 100 cc. of gastric juice. Dimethylamidoazobenzol and phenolphthalein were used as indicators since much of the work in the literature has been recorded in terms of them. With the former the end-point was taken to be the change from red to a frank yellow, with the latter the appearance of the first pinkish tint. Since we were dealing with a nonprotein test meal there usually was only a small difference between the readings with the two indicators.

4. Hydrogen ion concentration of the various specimens was determined by the colorimetric method. The procedure of Brown [1] enables one to make readings with small amounts of juice. Most of the values fell within the useful range of thymol blue, which has been shown to be satisfactory for work with stomach contents by Shohl and King [2] and which has been accepted by Clark [3] as free from salt and protein errors. For hydrogen ion concentrations outside the range of p_H 1.2 to p_H 3.0 the following indicators were used:

Methyl violet	p_H 1.0-1.2
Bromphenol blue	3.0-4.6
Methyl red	4.4-6.0
Bromcresol purple	5.2-6.8
Bromthymol blue	6.0-7.6

5. The degree of dilution of the test meal by gastric juice was determined as follows: It has been mentioned that 0.5 cc. of 1 per cent phenolphthalein was added to the test meal before injection. Parts of the fractions aspirated at ten minute intervals were made alkaline

1. Brown, J. H.: J. Lab. & Clin. Med. **9**:3 (Jan.) 1924.
2. Shohl, A. T., and King, J. H.: Bull. Johns Hopkins Hosp. **31**:158 (May) 1920.
3. Clark, W. M.: The Determination of Hydrogen Ion, Baltimore, 1920.

with a few drops of 10 per cent sodium hydroxid solution in order to bring out the purple of the dye. The concentration of the phenolphthalein in the specimen was then estimated by making a reading in a colorimeter against a standard of the same concentration as the test meal. The decrease in concentration of phenolphthalein in successive specimens indicates the percentage dilution of the test meal by gastric juice at various time intervals.

6. The volume of gastric juice secreted in each ten minute period was calculated as follows: The total amount of juice in the stomach and the concentration of phenolpththlein at the beginning and end of each ten minute period were known. Decrease in phenolphthalein concentration could conceivably be brought about either by secretion of gastric juice, which would act as a diluent, or by secretion combined with discharge of stomach contents through the pylorus. In any case the maximum possible amount of juice secreted would evidently be given by the following formula:

(1) $\left[\left(\frac{x}{y}\right)\times A\right] - A$ = maximum possible amount of juice secreted in ten minute period, in which

A = number of cubic centimeters of fluid in stomach at beginning of period,

x = concentration (percentage reading) of phenolphthalein at beginning of period, and

y = concentration of phenolpththalein at end of period.

Similarly,

(2) $B - \left[\left(\frac{y}{x}\right)\times B\right]$ = minimum possible amount of juice secreted in ten minute period, in which x and y are as above and B = total amount of stomach contents (cubic centimeters) at the end of period.

For example, if at the beginning of the period the stomach contained 37 cc. of material with a phenolphthalein concentration of 26 per cent, and if at the end of the period there was found to be 66 cc. of contents with a phenolphthalein of 13 per cent, then by formula (1) the maximum possible amount of juice secreted in the ten minute period was 37 cc. and the minimum possible amount was 33 cc. Obviously the actual amount secreted lies between these values.

In the protocols we have set down both the maximum and the minimum possible values, although an average of the two was used in calculating the amount of juice discharged from the stomach.

7. The amount of material discharged during each ten minute period was calculated by subtracting the total volume of stomach contents at the end of the period from the sum of the contents at the

beginning of the period and the amount of juice secreted. In the foregoing example 37 + 35 — 66 = 6 cc. (amount discharged).

8. The concentration of acid in the pure juice undiluted by test meal was calculated as follows: If, for example, the specimen aspirated from the stomach thirty minutes after the test meal has a phenolphthalein concentration of 30 per cent, then at this time 30 per cent of the stomach contents is made up of test meal and 70 per cent is gastric juice. If the titratable acidity of the specimen is 50 then the titratable acidity of the pure juice must be 71.4 ($\frac{50}{70} \times 100$).

9. In the titration of ferments the method we have used consisted in incubating at 37 C. for one-half hour 1 cc. of gastric juice with various quantities of normal human blood serum. The largest amount of serum digested as tested by precipitation with 20 per cent trichloracetic acid was taken to represent the degree of peptic activity. This method and the results obtained with it will be discussed at another time.

Several workers [4] have used procedures somewhat similar to the present one so far as a meal of weak alcohol to which phenolphthalein or another dye has been added is administered, and percentage dilutions of the dye are determined in samples aspirated at various intervals. These methods fail, however, to give the most important piece of information about gastric activity, namely, the volume of juice secreted and discharged. We have found that different persons may have the same percentage decrease in phenolphthalein when the amounts of juice secreted in the two cases represent the maximum and minimum extremes that may be encountered. This is, of course, due to the fact that dilution of dye depends not only on secretion but also on the rate of discharge.

The description of the foregoing procedure must be supplemented by a discussion of some difficulties and possible errors. In the first place it should be mentioned that a certain percentage of examinations—about 10 per cent—are vitiated by persistent regurgitation of bile after the test meal has been injected. If the examination is repeated at another time this difficulty is usually not reencountered. In the absence of visible bile staining it has seemed justifiable to assume that no duodenal regurgitation has taken place. A second possible source of error is incomplete aspiration of the stomach contents at the ten minute intervals. If only part of the juice is withdrawn the figures from which secretion and discharge are calculated will obviously be incorrect. Our impression is that by thorough suction applied with the subject on the right and left sides and in the dorsal position, all free fluid in the stom-

4. Heilmeyer, L.: Deutsches Arch. f. klin. Med. **148**:273, 1925. Lanz, W.: Arch. f. klin. Chir. **115**:294 (Feb.) 1921.

ach can be withdrawn. It is possible, however, that in certain instances of spasm, aspirations may be incomplete. The effect on gastric activity of withdrawing and reinjecting the stomach contents also is a matter for consideration; at any rate the present procedure approximates normal conditions more closely than complete drainage of the stomach at frequent intervals. Phenolphthalein has seemed quite satisfactory for measuring changes in concentration of the gastric juice. Colorimeter readings are readily made and the error is negligible. The dye is insoluble in acids and is not absorbed from the stomach.[5] Prolonged contact with gastric juice *in vitro* produces no alteration in the colorimetric readings. The greatest difficulty that we have encountered has been in certain cases in which the estimation of the quantity of gastric secretion is unsatisfactory owing to wide differences between the calculated maximum and minimum amounts. As a rule the differences are so small that the correct figure can be closely approximated by an average, as may be seen in the succeeding protocols. Occasionally, however, accurate figures cannot be obtained and one can only tell in a general way the amount of gastric secretion. The alcohol test meal seems to be a satisfactory stimulus to stomach secretion, and we have confined ourselves to its use in order to get comparative results. It would be quite possible, however, to use other soluble substances in larger or smaller amounts.

RESULTS

Approximately 100 examinations have been made by the foregoing method. For the most part they have been made in the case of people without digestive symptoms. A good deal of information has been obtained about the variations that may occur in such a group. At the present time, however, only a few cases will be described in order to illustrate the method and to indicate the type of information that may be obtained.

PROTOCOLS OF EXAMINATIONS[6]

EXAMINATION 1.—J. E., a normal boy, aged 19 years, had never had any digestive symptoms. He was examined Oct. 7, 1925, and again October 12. The results of the first test are shown in table 1 and chart 1; the results of the second test in table 2 and chart 2.

EXAMINATION 2.—B. S., a normal boy, aged 15 years, had never had any digestive symptoms (table 3 and chart 3). It may be noted that this person secreted much more gastric juice than J. E., although the degree of acidity was somewhat less.

5. Sollmann: A Manual of Pharmacology, Ed. 2, 1924, p. 208.

6. In the charts ordinates indicate amount of stomach contents and amount of secretion and discharge measured in cubic centimeters, and concentration of acid in terms of number of cubic centimeters of the tenth normal sodium hydroxid necessary to neutralize 100 cc. of pure gastric juice (phenolphthalein).

EXAMINATION 3.—J. S. was examined twice (tables 4 and 5, charts 4 and 5). This man, aged 50, had a marked bradycardia. There were no digestive symptoms. It is of interest that in this case of anacidity as much juice was secreted as in some instances of persons with normal acid, for example by J. E., on the second examination.

EXAMINATION 4.—G. W., a man, aged 49, was convalescent from bronchopneumonia. There were no digestive symptoms. The results of the test are shown in table 6 and chart 6.

EXAMINATION 5.—P. N., a man, aged 24, had had amebic dysentery several years before examination. At this time he was clinically well. There were no digestive symptoms (table 7 and chart 7).

EXAMINATION 6.—I. S. was a neurotic man, aged 38 (chart 8 and table 8). There were vague digestive symptoms which may have been due to a duodenal ulcer.

EXAMINATION 7.—A. W., a man, aged 47, had hysteria. The results of the test in his case (table 9 and chart 9) should be contrasted with those in I. S. Both men had a very low gastric juice, but I. S. secreted large amounts and retained fluid in his stomach, whereas A. W. secreted only small quantities of juice and emptied his stomach rapidly.

EXAMINATION 8.—J. C., a man, aged 35, convalescent from acute nephritis, had never had any digestive symptoms. Examination on two occasions (tables 10 and 11, charts 10 and 11) showed essentially the same result. There was an immediate great secretion of juice of low acidity followed by rapid emptying of the stomach and almost complete cessation of secretion.

EXAMINATION 9.—M. G. H. was a healthy woman, aged 28; the examination (table 12) showed the association of low acidity with hypermotility.

SUMMARY

A method is described whereby one may determine simultaneously the rate of gastric secretion and discharge, as well as other details of gastric function. The protocols given here illustrate the type of information that is obtained and indicate the useful possibilities of the method in studying the clinical pharmacology and pathology of the stomach.

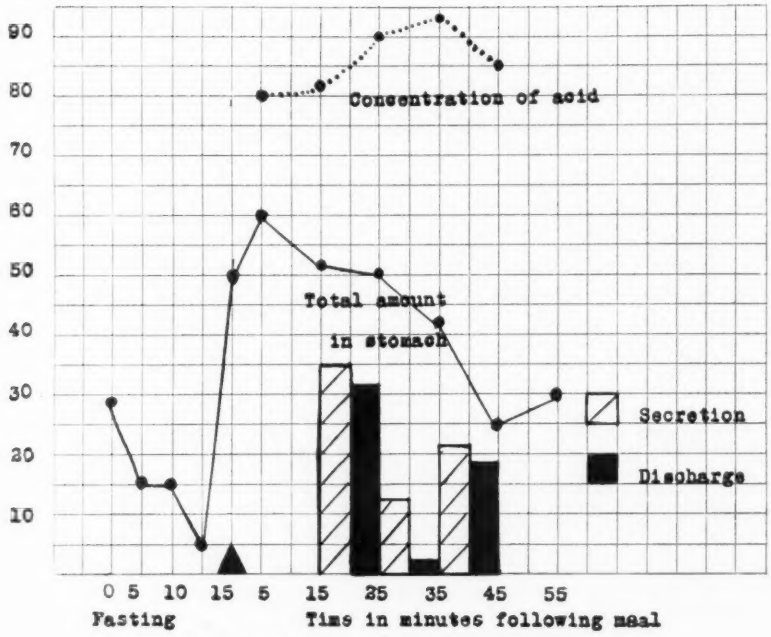

Chart 1.—Findings in examination 1, test 1.

TABLE 1.—*Results in Test 1, Examination 1*

Specimen	Obtained	Amount and Appearance	*pH*	Titratable Acidity in Terms of Cc. Tenth Normal Sodium Hydroxid: Dimethylamidoazobenzene	Titratable Acidity in Terms of Cc. Tenth Normal Sodium Hydroxid: Phenolphthalein	Total Stomach Contents, Cc.	Specimen Retained, Cc.	Amount Returned to Stomach, Cc.	Concentration of Phenolphthalein, per Cent	Amount of Juice Secreted in Ten Minute Period: Maximum, Cc.	Amount of Juice Secreted in Ten Minute Period: Minimum, Cc.	Amount of Juice Secreted in Ten Minute Period: Average, Cc.	Discharged in Ten Minute Period, Cc.	Acidity of Pure Juice
1	Fasting	29 cc. faintly bile tinged fluid with small amount of mucus	1.6	14	44	..	..	..	..	....	....	....	....	..
2	Fasting, 5 minutes after specimen 1	15 cc. faintly bile tinged fluid with small amount of mucus	1.4	58	70	..	..	..	..	....	....	....	....	..
3	Fasting, 10 minutes after specimen 1	15 cc. colorless fluid with some mucus	1.3	80	92	..	..	..	..	....	....	....	....	92
4	Fasting, 15 minutes after specimen 1	5 cc. colorless fluid with some mucus	1.2	87	99	..	.	..	..	....	....	....	....	99
5	5 min. after meal	Clear, limpid fluid	1.45	30	32	60	11	49	60	....	....	....	....	80
6	15 min. after meal	Clear, limpid fluid	1.25	54	56	53	13	40	31	45.5	26.0	35.7	31.0	81
7	25 min. after meal	Clear, limpid fluid	1.20	68	70	50	10	40	23	13.6	13.0	13.3	13.0	90
8	35 min. after meal	Clear, limpid fluid	1.15	78	80	42	9	33	14	25.0	17.0	21.0	19.0	93
9	45 min. after meal	Clear, limpid fluid	1.10	80	84	25	11	14	Trace	....	....	....	....	85
10	55 min. after meal	Heavily bile stained fluid	....	..	..	30	..	..	..	....	....	....	....	..

J. E., a boy aged 19 years, Oct. 7, 1925. Diagnosis: Normal control. There were no symptoms of digestive disturbance

Total fasting contents	29 cc.	Stomach "empty"	55 minutes
Fasting secretion during 10 minutes	From 20 to 30 cc.	Lowest *pH* (45 minutes)	1.10
Total secretion (30 minutes)	72 cc.	Highest free acid (45 minutes)	80
Largest amount secreted in 10 minutes	35.7 cc.	Highest total acid (45 minutes)	84
Largest amount in stomach during test	60 cc.	Highest acidity of pure juice (45 minutes)	93

Comment: A high degree of acidity; gradual steady emptying of stomach over period of 55 minutes when bile regurgitated; no great volume of secretion in spite of high acidity; fasting secretion approximated that during test both in quantity and in acidity

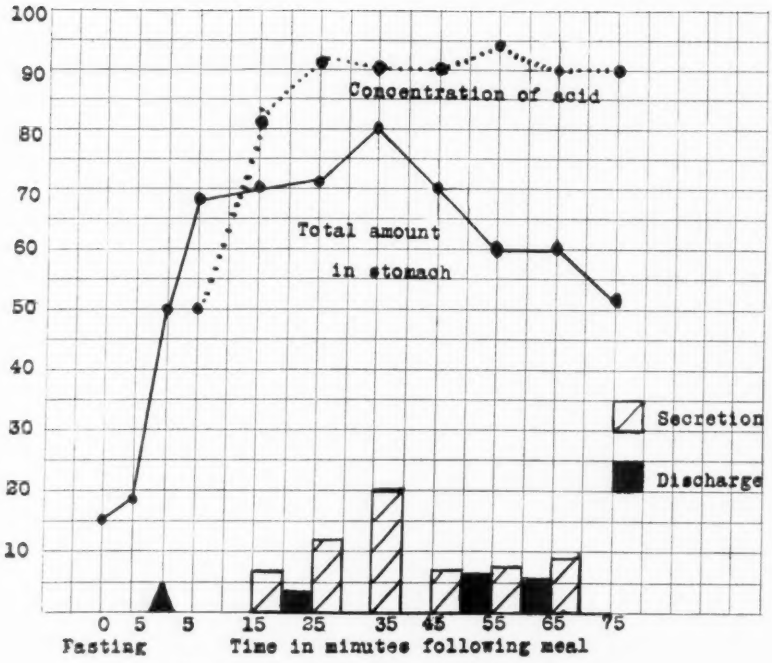

Chart 2.—Findings in test 1, examination 2.

TABLE 2.—*Results in Test 2, Examination 1*

Specimen	Obtained	Amount and Appearance	p_H	Titratable Acidity in Terms of Cc. Tenth Normal Sodium Hydroxid: Dimethylamidoazobenzene	Titratable Acidity in Terms of Cc. Tenth Normal Sodium Hydroxid: Phenolphthalein	Total Stomach Contents, Cc.	Specimen Retained, Cc.	Amount Returned to Stomach, Cc.	Concentration of Phenolphthalein, per Cent	Amount of Juice Secreted in Ten Minute Period: Maximum, Cc.	Amount of Juice Secreted in Ten Minute Period: Minimum, Cc.	Amount of Juice Secreted in Ten Minute Period: Average, Cc.	Discharged in Ten Minute Period, Cc.	Acidity of Pure Juice
1	Fasting.....	15 cc. clear fluid with bits of mucus	1.60	26	..	..	..	..	..	....	....	....	....	..
2	Fasting, 5 minutes after specimen 1	18 cc. clear fluid with bits of mucus	1.45	34	..	..	..	..	..	....	....	....	....	..
3	5 min. after meal	Clear fluid with bits of mucus	1.30	24	30	68	10	58	40	....	....	....	....	50
4	15 min. after meal	Clear fluid with bits of mucus	1.20	46	52	70	10	60	36	6.8	6.8	6.8	4.8	81
5	25 min. after meal	Clear fluid with bits of mucus	1.30	56	64	72	12	60	30	12.0	12.0	12.0	0	91
6	35 min. after meal	Clear fluid with bits of mucus	1.30	64	70	80 ?	10	70	22	20.0	20.0	20.0	0	90
7	45 min. after meal	Clear fluid with bits of mucus	1.20	68	72	70	10	60	20	7.7	7.0	7.3	7	90
8	55 min. after meal	Clear fluid with bits of mucus	1.15	72	78	70	10	60	17 ?	10.2	10.0	10.0	0	94
9	65 min. after meal	Clear fluid with bits of mucus	1.15	74	78	62	10	52	15	7.8	7.8	7.8	6	91
10	75 min. after meal	Clear fluid with bits of mucus	1.15	74	78	60	..	..	13	8.0	8.0	8.0	0	90

J. E., Oct. 12, 1925

Total fasting contents	15 cc.	Stomach "empty" (still contained 60 cc. at end of 75 minutes)	
Fasting secretion (5 minutes)	18 cc.	Lowest p_H (55 minutes)	1.15
Total secretion (70 minutes)	72 cc.	Highest free acid (65 minutes)	74
Largest amount secreted in 10 minutes	20 cc.	Highest total acid (55 minutes)	78
Largest amount in stomach during test	80 cc.	Highest acidity of pure juice	94

Comment: Findings somewhat different from previous examination; acidity high (about same as before); stomach emptied much more slowly and still contained 60 cc. at 75 minutes, although quantity of juice secreted per 10 minute period was less than on previous examination

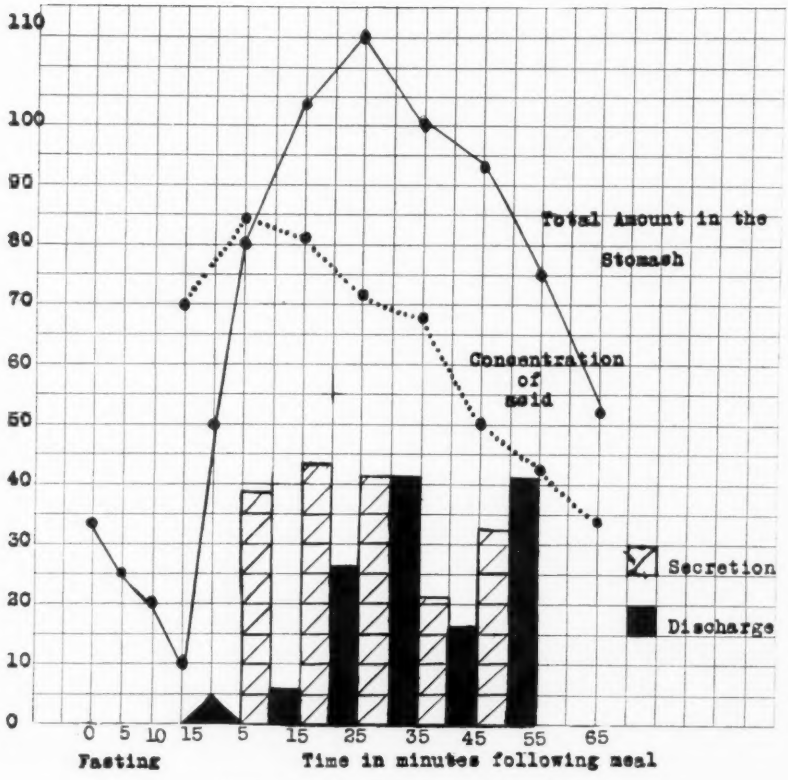

Chart 3.—Findings in examination 2.

TABLE 3.—*Results in Examination 2*

Specimen	Obtained	Amount and Appearance	p_H	Titratable Acidity in Terms of Cc. Tenth Normal Sodium Hydroxid: Dimethylamidoazobenzene	Titratable Acidity in Terms of Cc. Tenth Normal Sodium Hydroxid: Phenolphthalein	Total Stomach Contents, Cc.	Specimen Retained, Cc.	Amount Returned to Stomach, Cc.	Concentration of Phenolphthalein, per Cent	Amount of Juice Secreted in Ten Minute Period: Maximum, Cc.	Amount of Juice Secreted in Ten Minute Period: Minimum, Cc.	Amount of Juice Secreted in Ten Minute Period: Average, Cc.	Discharged in Ten Minute Period, Cc.	Acidity of Pure Juice
1	Fasting.....	34 cc. deeply bile stained fluid	...	..	..	..	..	..	..	....	....	....	....	..
2	Fasting, 5 minutes after specimen 1	25 cc. slightly bile stained fluid with much mucus	1.7	20	30	..	..	..	..	....	....	....	....	..
3	Fasting, 10 minutes after specimen 1	20 cc. moderately bile tinged fluid with some mucus	...	..	..	..	..	..	..	....	.. .	....	....	..
4	Fasting, 15 minutes after specimen 1	18 cc. moderately bile tinged fluid with some mucus	...	60	70	..	..	..	..	....	....	....	....	70
5	5 min. after meal	Clear, colorless fluid; some mucus	1.55	28	32	80	70	70	63	....	....	....	....	84
6	15 min. after meal	Clear, colorless fluid; some mucus	1.45	46	50	104	10	94	39	40.6	39.0	39.8	5.8	81
7	25 min. after meal	Clear, colorless fluid; some mucus	1.38	52	54	110	10	100	26	47.0	37.0	42.0	26.0	72
8	35 min. after meal	Clear, colorless fluid; some mucus	1.40	50	56	100	10	90	17	50.0	33.0	41.5	41.5	67
9	45 min. after meal	Clear, colorless fluid; some mucus	1.42	38	42	94	11	83	12	29.7	11.0	20.3	16.3	50
10	55 min. after meal	Clear, colorless fluid; some mucus	1.50	34	40	75	11	64	8	41.5	25.0	33.0	41.0	43
11	65 min. after meal	Clear, colorless fluid; some mucus	1.55	30	34	52	..	..	Trace	....	....	....	....	..

B. S., a boy, aged 15 years. Diagnosis: Healthy boy; normal control

Total fasting contents	34 cc.	Stomach "empty" (still contained 52 cc. at 65 minutes)	
Fasting secretion during 10 minutes	From 25 to 40 cc.	Lowest p_H (25 minutes)	1.38
Total secretion (50 minutes)	177 cc.	Highest free acid (25 minutes)	52
Largest amount secreted in 10 minutes	42 cc.	Highest total acid (35 minutes)	56
Largest amount in stomach during test	110 cc.	Highest acidity of pure juice	84

Comment: Titratable acidity high but not excessive; p_H did not fall as low as in many normal people; there was, however, an abundant secretion of juice, with increasing stomach content until 25 minutes and then a gradual emptying; the steady fall in acidity with decrease of secretion was of interest; fasting secretion was abundant and highly acid

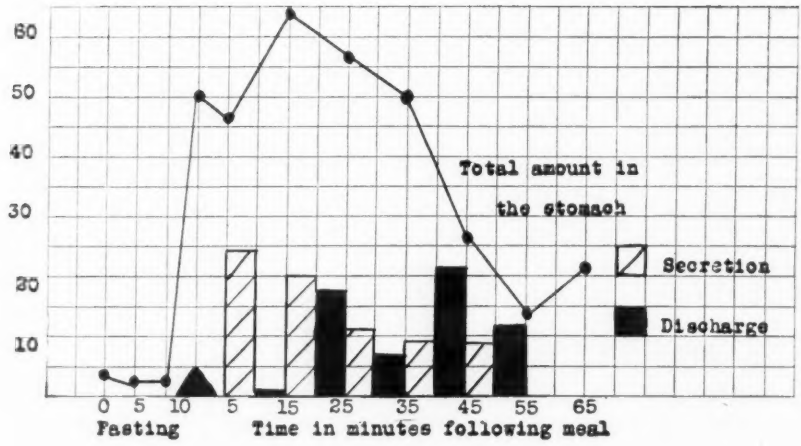

Chart 4.—Findings in test 1, examination 3.

TABLE 4.—*Results in Test 1, Examination 3*

Specimen	Obtained	Amount and Appearance	p_H	Titratable Acidity in Terms of Cc. Tenth Normal Sodium Hydroxid: Dimethylamidoazobenzene	Titratable Acidity in Terms of Cc. Tenth Normal Sodium Hydroxid: Phenolphthalein	Total Stomach Contents, Cc.	Specimen Retained, Cc.	Amount Returned to Stomach, Cc.	Concentration of Phenolphthalein, per Cent	Amount of Juice Secreted in Ten Minute Period: Maximum, Cc.	Amount of Juice Secreted in Ten Minute Period: Minimum, Cc.	Amount of Juice Secreted in Ten Minute Period: Average, Cc.	Discharged in Ten Minute Period, Cc.	Acidity of Pure Juice
1	Fasting.....	4 cc. practically pure mucus	...	0.0	2.0	..	..	..	..	....	....	....	....	..
2	Fasting, 5 minutes after specimen 1	3 cc. practically pure mucus	7.2	0.0	2.0	..	..	..	..	....	....	....	....	..
3	Fasting, 10 minutes after specimen 1	2.5 cc. practically pure mucus	7.4	0.0	2.0	..	..	..	..	....	....	....	....	..
4	5 min. after meal	Clear fluid with much mucus	6.9	0.0	2.0	46	6	40	83	....	....	....	....	..
5	15 min. after meal	Clear fluid with much mucus	6.6	0.0	4.0	64	11	53	50	26.5	23.5	24.5	1.0	..
6	25 min. after meal	Clear fluid with much mucus	6.5	0.0	4.0	56	10	46	35	22.5	17.0	20.0	17.0	..
7	35 min. after meal	Clear fluid with much mucus	6.4	0.0	4.0	50	11	39	28	11.5	10.0	11.0	7.0	..
8	45 min. after meal	Clear fluid with much mucus	6.6	0.0	4.0	26	7	19	21	13.0	5.5	9.5	22.0	..
9	55 min. after meal	Clear fluid with much mucus	6.6	0.0	4.0	14	8	6	14	9.5	4.5	7.0	12.0	..
10	65 min. after meal	Clear fluid with much mucus	6.7	0.0	4.0	22	..	..	Trace	....	....	....	....	..

S., a man, aged 50, Oct. 5, 1925. Diagnosis: Bradycardia. There were no symptoms of digestive disturbance

Total fasting contents	4.0 cc.	Stomach "empty"	65 minutes
Fasting secretion during 10 minutes	5.5 cc.	Lowest p_H (35 minutes)	6.4
Total secretion (50 minutes)	72.0 cc.	Highest free acid	0.0
Largest amount secreted in 10 minutes	24.5 cc.	Highest total acid	4.0
Largest amount in stomach during test	64.0 cc.		

Comment: From standpoint of titratable acid, this case is one of complete anacidity; however, the p_H falls to 6.4, which indicates some increase of acidity during test; there is a gradual steady emptying of stomach over period of 65 minutes; the total amount of secretion is relatively low; fasting secretion very scant

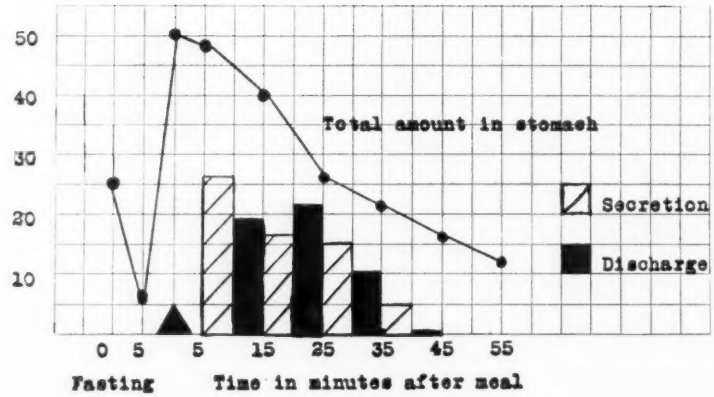

Chart 5.—Findings in test 2, examination 3.

TABLE 5.—*Results in Test 2, Examination 3*

Specimen	Obtained	Amount and Appearance	p_H	Titratable Acidity in Terms of Cc. Tenth Normal Sodium Hydroxid: Dimethylamidoazobenzene	Titratable Acidity in Terms of Cc. Tenth Normal Sodium Hydroxid: Phenolphthalein	Total Stomach Contents, Cc.	Specimen Retained, Cc.	Amount Returned to Stomach, Cc.	Concentration of Phenolphthalein, per Cent	Amount of Juice Secreted in Ten Minute Period: Maximum, Cc.	Amount of Juice Secreted in Ten Minute Period: Minimum, Cc.	Amount of Juice Secreted in Ten Minute Period: Average, Cc.	Discharged in Ten Minute Period, Cc.	Acidity of Pure Juice
1	Fasting	25 cc. turbid white fluid with particles of mucus	7.4	0.0	..	..	..	..	..	....	....	....	....	..
2	Fasting, 5 minutes after specimen 1	6 cc. turbid white fluid with particles of mucus	7.2	0.0	..	..	..	..	..	....	....	....	....	..
3	5 min. after meal	Clear fluid with bits of mucus	6.8	0.0	..	47	13	34	64	....	....	....	....	..
4	15 min. after meal	Clear fluid with bits of mucus	6.2	0.0	..	40	9	31	33	31.5	20.0	25.5	19.5	..
5	25 min. after meal	Clear fluid with bits of mucus	5.5	0.0	..	26	9.5	17.5	21	17.5	16.0	16.7	21.0	..
6	35 min. after meal	Clear fluid with bits of mucus	6.5	0.0	..	22	11	11	10	18.5	12.0	15.0	10.0	..
7	45 min. after meal	Clear fluid with bits of mucus	6.8	0.0	..	16	8	8	7	5.0	5.0	5.0	0.0	..
8	55 min. after meal	Clear fluid with bits of mucus	7.0	0.0	..	12	..	..	Trace	....	....	....	....	..

S., Oct. 11, 1925

Total fasting contents	25 cc.	Stomach "empty"	55 minutes
Fasting secretion during 10 minutes	12 cc.	Lowest p_H	5.5
Total secretion (40 minutes)	62 cc.	Highest free acid	0.0
Largest amount secreted in 10 minutes	25 cc.	Highest total acid	...
Largest amount in stomach during test	47 cc.		

Comment: Findings essentially identical with those on previous examination

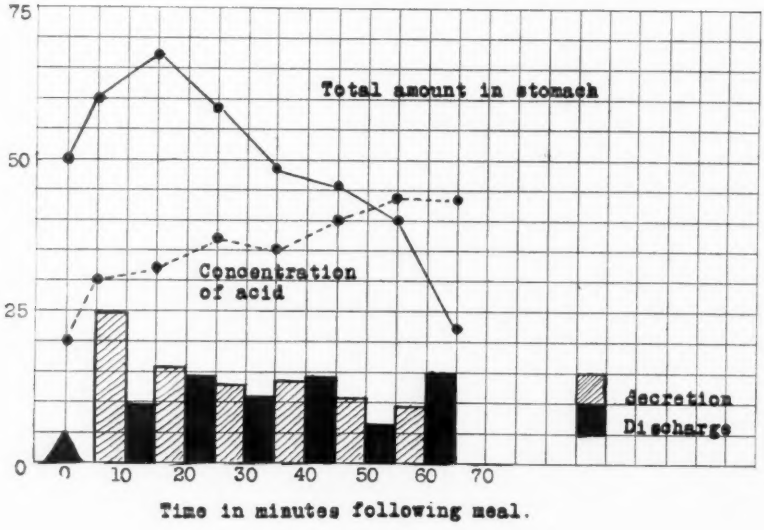

Chart 6.—Findings in examination 4.

TABLE 6.—*Results in Examination 4*

Specimen	Obtained	Amount and Appearance	p_H	Titratable Acidity in Terms of Cc. Tenth Normal Sodium Hydroxid: Dimethylamidoazobenzene	Titratable Acidity in Terms of Cc. Tenth Normal Sodium Hydroxid: Phenolphthalein	Total Stomach Contents, Cc.	Specimen Retained, Cc.	Amount Returned to Stomach, Cc.	Concentration of Phenolphthalein, per Cent	Amount of Juice Secreted in Ten Minute Period: Maximum, Cc.	Amount of Juice Secreted in Ten Minute Period: Minimum, Cc.	Amount of Juice Secreted in Ten Minute Period: Average, Cc.	Discharged in Ten Minute Period, Cc.	Acidity of Pure Juice
1	Fasting.....	Small amount of clear mucus	....	..	..	..	..	..	..	....	....	....	....	..
2	Fasting, 5 minutes after specimen 1	7 cc. clear mucus.....	....	..	..	..	..	..	..	....	....	....	....	..
3	Fasting, 10 minutes after specimen 1	5 cc. clear mucus	....	..	..	..	..	..	..	....	....	....	....	..
4	Fasting, 15 minutes after specimen 1	5 cc. clear fluid with mucus	2.05	10	20	..	..	..	..	....	....	....	....	20
5	5 min. after meal	Clear, limpid fluid.....	2.10	6	10	60	8	52	66	....	....	....	....	30
6	15 min. after meal	Clear, limpid fluid.....	1.96	11	17	67	10	57	44	26	23	24.5	9.5	32
7	25 min. after meal	Clear, limpid fluid.....	1.80	18	24	58	12	46	34	16.5	14.0	15.7	14.7	37
8	35 min. after meal	Clear, limpid fluid.....	1.70	20	26	48	11	37	26	13.8	12.0	13.0	11.0	35
9	45 min. after meal	Clear, limpid fluid.....	1.65	23	33	46	11	33	19	13.3	13.0	13.0	14.0	40
10	55 min. after meal	Clear, limpid fluid.....	1.60	30	37.5	40	12	28	14	12.2	11.0	11.6	7.0	43
11	65 min. after meal	Clear, limpid fluid.....	1.55	32	38	22	..	..	10	11.0	7.0	9.0	15.0	42

G. W., a man, aged 49. Diagnosis: Convalescent from bronchopneumonia; no digestive symptoms

Total fasting contents.....	A few cc.	Stomach "empty"	65 minutes
Fasting secretion during 10 minutes.....	10 cc.	Lowest p_H (65 minutes).....	1.55
Total secretion (60 minutes).....	87 cc.	Highest free acid (65 minutes).....	32
Largest amount secreted in 10 minute period.....	24.5 cc.	Highest total acid (65 minutes).....	38
Largest amount in stomach during test.....	67 cc.	Highest acidity of pure juice.....	..

Comment: Acidity of juice increased gradually and steadily but never reached a high value; the stomach emptied slowly and rather uniformly; at first a good deal of juice was secreted—the quantity in the ten minute periods steadily diminished, fasting secretions scanty and of low acidity

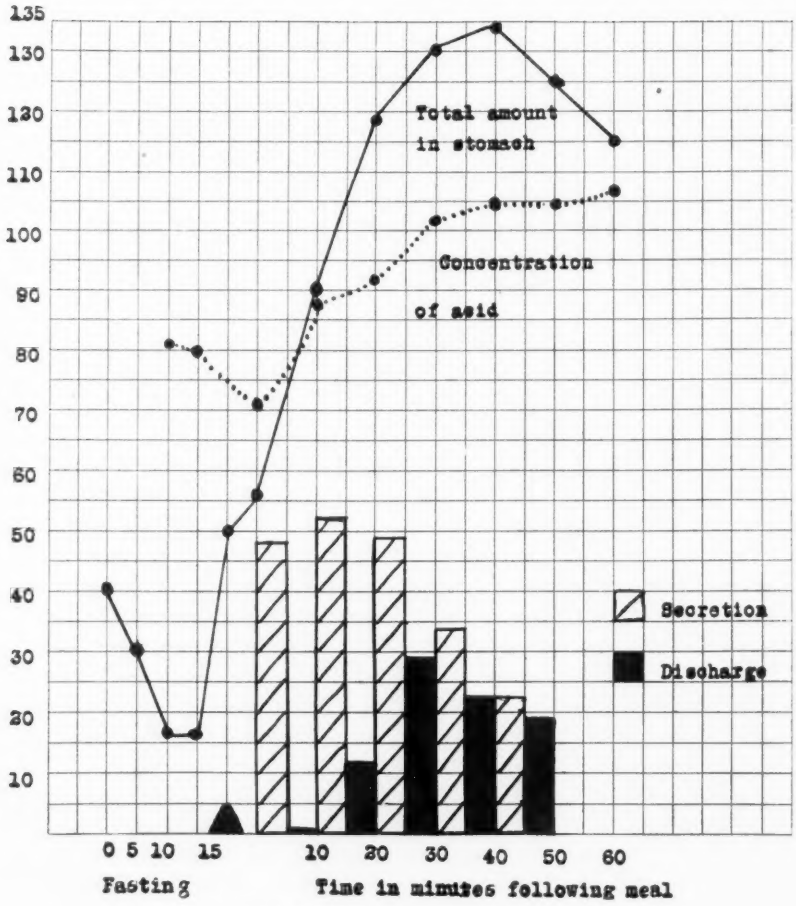

Chart 7.—Findings in examination 5.

TABLE 7.—*Results in Examination 5*

Specimen	Obtained	Amount and Appearance	p_H	Titratable Acidity in Terms of Cc. Tenth Normal Sodium Hydroxid: Dimethylamidoazobenzene	Titratable Acidity in Terms of Cc. Tenth Normal Sodium Hydroxid: Phenolphthalein	Total Stomach Contents, Cc.	Specimen Retained, Cc.	Amount Returned to Stomach, Cc.	Concentration of Phenolphthalein, per Cent	Amount of Juice Secreted in Ten Minute Period: Maximum, Cc.	Amount of Juice Secreted in Ten Minute Period: Minimum, Cc.	Amount of Juice Secreted in Ten Minute Period: Average, Cc	Discharged in Ten Minute Period, Cc.	Acidity of Pure Juice
1	Fasting	40 cc. bile	....	..	..	..	..	..	..	....	....	....	....	..
2	Fasting, 5 minutes after specimen 1	30 cc. moderately bile tinged fluid	....	..	..	..	..	..	..	....	....	....	....	..
3	Fasting, 10 minutes after specimen 1	16 cc. slightly bile tinged fluid	1.2	78	82	..	..	..	..	....	....	....	....	82
4	Fasting, 15 minutes after specimen 1	16 cc. slightly bile tinged fluid	1.2	72	80	..	..	..	..	....	....	....	....	80
5	Immediately after meal	Clear, colorless fluid	1.9	16	20	56	13	43	72	....	....	....	....	71
6	10 min. after meal	Clear, colorless fluid	1.25	50	58	90	12	78	34	47.3	47.3	47.3	0	87
7	20 min. after meal	Clear, colorless fluid	1.15	70	74	118	9	111	20	54.6	50.0	52.0	12	92
8	30 min. after meal	Clear, colorless fluid	1.10	78	88	130	10	120	13	54.5	44.0	49.0	28	101
9	40 min. after meal	Clear, colorless fluid	1.10	84	94	133	11	122	10	36.0	31.0	33.5	22.5	104
10	50 min. after meal	Clear, colorless fluid	1.05	88	96	125	9	114	8	24.4	21.0	22.5	19.5	104
11	60 min. after meal	Clear, colorless fluid	1.05	94	102	115	..	....	4 ?	....	....	....	....	106

P. N., a man, aged 24. Diagnosis: Old amebic dysentery (inactive); no gastric symptoms

Total fasting contents	40 cc.	Stomach "empty" (still contained 115 cc. at 60 minutes)	
Fasting secretion during 10 minutes	32 cc.	Lowest p_H (50 minutes)	1.05
Total secretion (50 minutes)	204 cc.	Highest free acid (60 minutes)	94
Largest amount secreted in 10 minutes	52 cc.	Highest total acid (60 minutes)	102
Largest amount in stomach during test	133 cc.	Highest acidity of pure juice	106

Comment: Prompt secretion of large amounts of highly acid juice; acidity increased steadily during experiment, whereas volume secreted diminished; discharge at first was much below secretion and volume of fluid in stomach rose to 133 cc. and then decreased; fasting secretion abundant and highly acid

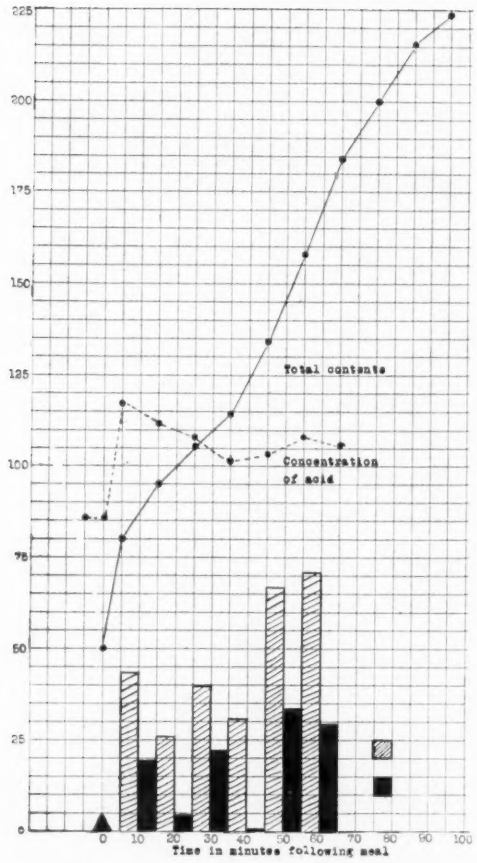

Chart 8.—Findings in examination 6.

TABLE 8.—*Results in Examination 6*

Specimen	Obtained	Amount and Appearance	*pH*	Titratable Acidity in Terms of Cc. Tenth Normal Sodium Hydroxid: Dimethylamidoazobenzene	Titratable Acidity in Terms of Cc. Tenth Normal Sodium Hydroxid: Phenolphthalein	Total Stomach Contents, Cc.	Specimen Retained, Cc.	Amount Returned to Stomach, Cc.	Concentration of Phenolphthalein, per Cent	Amount of Juice Secreted in Ten Minute Period: Maximum, Cc.	Amount of Juice Secreted in Ten Minute Period: Minimum, Cc.	Amount of Juice Secreted in Ten Minute Period: Average, Cc.	Discharged in Ten Minute Period, Cc.	Acidity of Pure Juice
1	Fasting.....	50 cc. clear fluid, slightly bile tinged	1.20	80	86	..	..	..	..	....	....	....	....	86
2	Fasting, 5 minutes after specimen 1	25 cc. clear fluid, faint bile tinge	1.20	80	86	..	..	..	..	....	....	....	....	86
3	5 min. after meal	Clear, limpid fluid.....	1.25	64	68	80	9	71	42	....	....	....	....	117
4	15 min. after meal	Clear, limpid fluid.....	1.20	80	84	95	11	84	25	48.2	38.5	43.0	19	112
5	25 min. after meal	Clear, limpid fluid.....	1.15	84	88	106	10	96	19	26.0	26.0	26.0	4	108
6	35 min. after meal	Clear, limpid fluid.....	1.10	88	92	114	11	103	13	44.1	36.0	40.0	22	101
7	45 min. after meal	Clear, limpid fluid.....	1.10	90	94	134	10	124	10	31.0	31.0	31.0	0	104
8	55 min. after meal	Clear, limpid fluid.....	1.05	98	102	158	11	147	6	74.0	60.0	67.0	33	108
9	65 min. after meal	Clear, limpid fluid.....	1.05	98	102	189	10	179	4	79.0	63.0	71.0	29	106
10	75 min. after meal	Clear, limpid fluid.....	1.05	98	102	200	10	190	Trace	....	....	....	..	...
11	85 min. after meal	Clear, limpid fluid.....	1.05	98	102	216	11	205	Trace	....	....	....	..	...
12	95 min. after meal	Clear, limpid fluid.....	1.05	98	102	223	..	...	Trace	....	....	....	..	...

1. S., a man, aged 38. Diagnosis: Gastric neurosis; duodenal ulcer ?

Total fasting contents	50 cc.	Stomach "empty" (still 223 cc. of 95 minutes)	
Fasting secretion during 10 minutes	50 cc.?	Lowest *pH* (55 minutes)	1.05
Total secretion (60 minutes)	278 cc.	Highest free acid (55 minutes)	98
Largest amount secreted in 10 minutes	67 cc.	Highest total acid (55 minutes)	102
Largest amount of juice in stomach during test	223 cc.	Highest acidity of pure juice	117

Comment: Prompt secretion of large amounts of very acid juice which decreased somewhat in acidity but increased in amount as test progressed; only slight discharge so that large amount of fluid accumulated in stomach; fasting secretion abundant and very acid

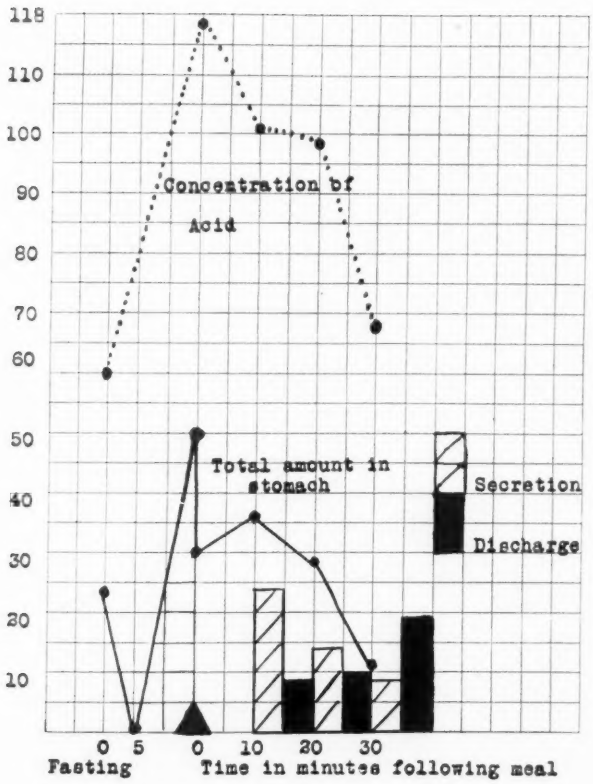

Chart 9.—Findings in examination 7.

TABLE 9.—*Results in Examination 7*

Specimen	Obtained	Amount and Appearance	p_H	Titratable Acidity in Terms of Cc. Tenth Normal Sodium Hydroxid: Dimethylamidoazobenzene	Titratable Acidity in Terms of Cc. Tenth Normal Sodium Hydroxid: Phenolphthalein	Total Stomach Contents, Cc.	Specimen Retained, Cc.	Amount Returned to Stomach, Cc.	Concentration of Phenolphthalein, per Cent	Amount of Juice Secreted in Ten Minute Period: Maximum, Cc.	Amount of Juice Secreted in Ten Minute Period: Minimum, Cc.	Amount of Juice Secreted in Ten Minute Period: Average, Cc.	Discharged in Ten Minute Period, Cc.	Acidity of Pure Juice
1	Fasting	24 cc. fluid and mucus	1.10	48	60	..	..	..	..	....	....	....	....	60
2	Fasting, 5 minutes after meal	Nothing obtained	....	..	..	..	..	..	..	....	....	....	....	..
3	Immediately after meal	Clear fluid	1.80	22	26	30	10	20	78	....	....	....	....	118
4	10 minutes after meal	Clear fluid	1.15	55	61	36	11	25	30	26.0	23.0	24.5	8.5	101
5	20 minutes after meal	Clear fluid	1.10	78	84	29	9	20	15	14.0	14.0	14.0	10.0	98
6	30 minutes after meal	Clear fluid	1.20	55	61	9	..	..	9 ?	13.0	4.0	8.5	18.5	67

A. W., a man, aged 47. Diagnosis: Hysteria; no evidence of organic disease

Total fasting contents	24 cc.	Stomach "empty"	30 minutes
Fasting secretion (10 minutes)	0 cc.?	Lowest p_H (20 minutes)	1.10
Total secretion (30 minutes)	47 cc.	Highest free acid (20 minutes)	78
Largest amount secreted in 10 minutes	24.5 cc.	Highest total acid (20 minutes)	84
Largest amount in stomach during test	36 cc.	Highest acidity of pure juice	118

Comment: Following test meal there was a prompt secretion of extremely acid juice in moderate amount; this steadily decreased in amount and acidity, and stomach, which emptied rapidly, was void in 30 minutes; very slight amount of fasting secretion of moderate acidity

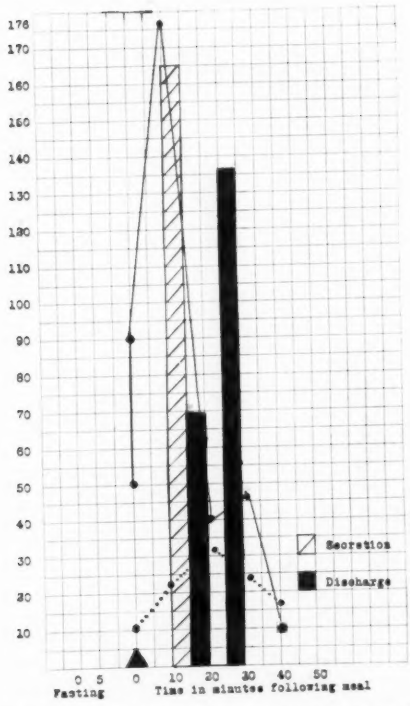

Chart 10.—Findings in test 1, examination 8.

TABLE 10.—*Results in Test 1, Examination 8*

Specimen	Obtained	Amount and Appearance	p_H	Titratable Acidity in Terms of Cc. Tenth Normal Sodium Hydroxid: Dimethyl-amidoazo-benzene	Titratable Acidity in Terms of Cc. Tenth Normal Sodium Hydroxid: Phenol-phthalein	Total Stomach Contents, Cc.	Specimen Retained, Cc.	Amount Returned to Stomach, Cc.	Concentration of Phenol-phthalein, per Cent	Amount of Juice Secreted in Ten Minute Period: Maximum, Cc.	Amount of Juice Secreted in Ten Minute Period: Minimum, Cc.	Amount of Juice Secreted in Ten Minute Period: Average, Cc.	Discharged in Ten Minute Period, Cc.	Acidity of Pure Juice
1	Fasting	Questionable amount of mucus	...	..	..	..	..	..	..	....	....	....	....	..
2	Fasting, 5 minutes after specimen 1	Nothing obtained	...	..	..	..	..	..	..	....	....	....	....	..
3	Immediately after meal	Clear fluid with a great deal of thin mucus	2.9	2	6	90	10	80	40	....	....	....	....	10
4	10 minutes after meal	Clear fluid with a great deal of thin mucus	2.0	12	20	176	12	164	11	200	130	165	69	22
5	20 minutes after meal	Marked bile tinged, thin mucus	...	18	32	40	10	30	0	?	?	?	136+	32
6	30 minutes after meal	Clear fluid with a great deal of mucus	1.5	16	24	46	12	34	0	....	....	....	....	24
7	40 minutes after meal	Clear fluid with a great deal of mucus	3.1	2	16	10	..	..	0	....	....	....	....	16

J. C., a man, aged 35. Diagnosis: Acute nephritis—convalescent; no gastric symptoms of any sort; had been on salt-free diet for several weeks

Total fasting contents	0 cc.?	Stomach "empty"	20 minutes
Fasting secretion during 10 minutes	0 cc.?	Lowest p_H (30 minutes)	1.5
Total secretion (10 minutes)	165 cc.	Highest free acid (20 minutes)	18
Largest amount secreted in 10 minutes	165 cc.	Highest total acid (20 minutes)	32
Largest amount in stomach during test	176 cc.	Highest acidity of pure juice	32

Comment: A distinctly abnormal reaction; the juice consisted entirely of a thin mucus; test meal followed by a tremendous secretion of juice of very low acidity; rapid emptying of stomach

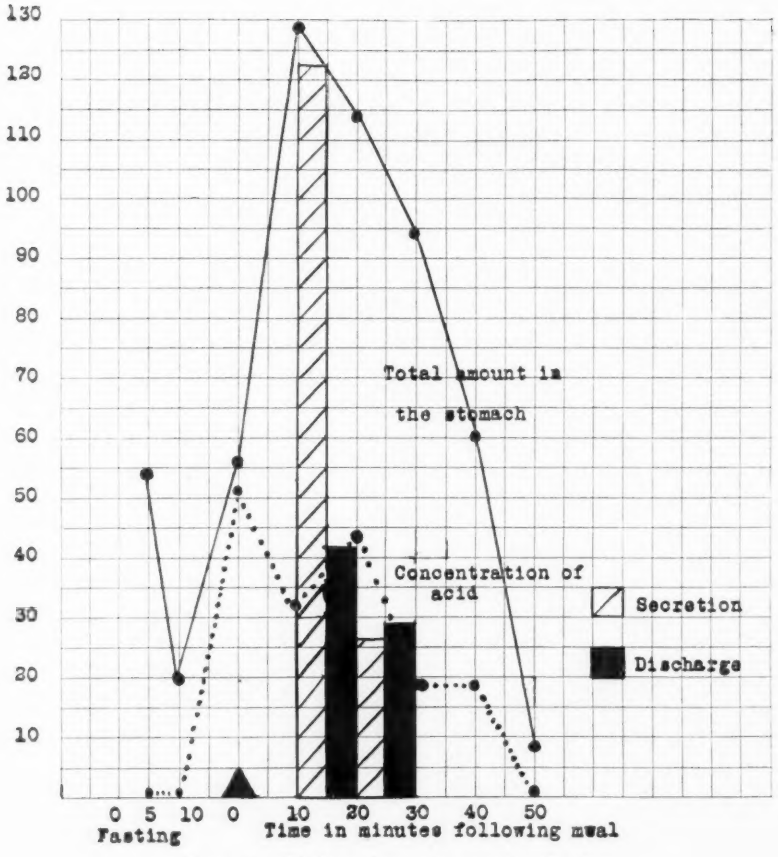

Chart 11.—Findings in test 2, examination 8.

TABLE 11.—*Results in Test 2, Experiment 8*

Specimen	Obtained	Amount and Appearance	p_H	Titratable Acidity in Terms of Cc. Tenth Normal Sodium Hydroxid: Dimethylamidoazobenzene	Titratable Acidity in Terms of Cc. Tenth Normal Sodium Hydroxid: Phenolphthalein	Total Stomach Contents, Cc.	Specimen Retained, Cc.	Amount Returned to Stomach, Cc.	Concentration of Phenolphthalein, per Cent	Amount of Juice Secreted in Ten Minute Period: Maximum, Cc.	Amount of Juice Secreted in Ten Minute Period: Minimum, Cc.	Amount of Juice Secreted in Ten Minute Period: Average, Cc.	Discharged in Ten Minute Period, Cc.	Acidity of Pure Juice
1	Fasting	....	...	..	..	..	..	..	..	....	....	....	....	..
2	Fasting, 5 minutes after specimen 1	54 cc. thin mucus	...	0	..	..	..	..	..	....	....	....	....	..
3	Fasting, 10 minutes after specimen 1	20 cc. thin mucus	5.6	0	6	..	..	..	..	....	....	....	....	..
4	Immediately after meal	Clear, thin mucus	1.4	24	30	56	10	46	42	....	....	....	....	51
5	10 minutes after meal	Clear, thin mucus	1.7	20	28	128	12	116	10	147	98	123	41	33
6	20 minutes after meal	Clear, thin mucus	1.4	26	40	114	10	104	8	29	23	26	28	43
7	30 minutes after meal	Clear, thin mucus	2.2	6	18	94	12	82	Trace	....	....	....	....	18
8	40 minutes after meal	Clear, thin mucus	1.9	6	18	60	12	48	Trace	....	....	....	....	18
9	50 minutes after meal	Clear, thin mucus	2.4	..	..	8	..	..	0	....	....	....	....	..

J C., a man, aged 35. Diagnosis: Acute nephritis—convalescent; no gastric symptoms of any sort; had been on salt-free diet for several weeks

Total fasting contents	? cc.	Stomach "empty"	50 minutes
Fasting secretion during 10 minutes	74 cc.	Lowest p_H (20 minutes)	1.4
Total secretion (20 minutes)	149 cc.	Highest free acid (20 minutes)	26
Largest amount secreted in 10 minutes	123 cc.	Highest total acid (20 minutes)	40
Largest amount in stomach during test	128 cc.	Highest acidity of pure juice	43

Comment: Reaction showed essentially the same peculiarities as on previous occasion

TABLE 12.—*Results in Examination 9*

Specimen	Obtained	Amount and Appearance	p_H	Titratable Acidity in Terms of Cc. Tenth Normal Sodium Hydroxid: Dimethylamidoazobenzene	Titratable Acidity in Terms of Cc. Tenth Normal Sodium Hydroxid: Phenolphthalein	Total Stomach Contents, Cc.	Specimen Retained, Cc.	Amount Returned to Stomach, Cc.	Concentration of Phenolphthalein, per Cent
1	Fasting	20 cc. thin fluid with bits of mucus	2.1	10	26	..	..	..	..
2	Fasting, 5 minutes after specimen 1	Nothing obtained	...	..	..	..	..	..	..
3	Immediately after meal	Clear fluid	4.2	0	2	25	10	15	64
4	10 minutes after meal	Nothing obtained	...	..	..	..	..	..	..

M. G. H., a woman, aged 28. Diagnosis: Healthy control; test meal 2 years before showed "anacidity"; no definite digestive symptoms

Total fasting contents	20 cc.	Largest amount in stomach	25 cc.
Fasting secretion (10 minutes)	0 cc.	Stomach "empty"	5 to 10 minutes
Total secretion	?		

Comment: Extreme subacidity; practically no gastric secretion; marked rapidity of emptying

THE RELATION OF THE ERYTHROCYTE SEDIMENTATION REACTION TO THE ABILITY OF FLOCCULATION OF THE PLASMA AND SERUM *

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Several tests have been recently advocated for the determination of "activity" in tuberculosis. The more prominently mentioned are the Frisch and Starlinger,[1] Gerlóczy,[2] Mátéfy,[3] Darányi,[4] and erythrocyte sedimentation [5] reactions. These tests are not specific for tuberculosis and are obtainable in all conditions in which there is an accompanying tissue destruction, their utility being comparable to that of a clinical thermometer. We have had occasion to observe the sedimentation reaction on several hundred tuberculous patients and have been impressed with its usefulness in gaging the toxicity of a tuberculous process. When used in conjunction with other clinical and laboratory means of investigation, the test offers a valuable addition to the study of a patient's progress. The results that have been reported from the use of the other named tests, although not as favorable as those that have been obtained with the sedimentation reaction, nevertheless seem to indicate that the physicochemical structure of the blood, especially that of the unformed elements, is modified in some way during disease, the change being more or less proportional to the severity of the disease process. Although a similarity between these tests has been noted by the originators of the several methods, they have been, with a few exceptions, applied singly with little attempt to evaluate them from a study of the same sample of blood. The present study was therefore undertaken to determine the relationship between these tests, the accuracy and ease of their execution and their relative clinical value.

The detailed procedures of the several methods are obtainable in the original papers so that only a brief outline will be given here:

METHODS

Frisch and Starlinger Test.—Two-tenths cubic centimeter of citrated plasma is added to an equal amount of concentrated sodium chloride solution, shaken once and the degree of flocculation observed

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1. Frisch, A. V., and Starlinger, W.: Med. Klin. **18**:247 (Feb. 19) 1922.
2. Von Gerlóczy, G.: Klin. Wchnschr. **1**:2134 (Oct. 21) 1922.
3. Mátéfy, L.: Med. Klin. **19**:725 (May 27) 1923.
4. Von Darányi, J.: Deutsche med. Wchnschr. **48**:553 (April 28) 1922.
5. Fahraeus, R.: Biochem. Ztschr. **89**:355, 1918.

at the end of three minutes. The results are designated as —, ±, +, + +, + + + and + + + +, depending on the degree of flocculation.

Gerlóczy Test.—Three-tenths cubic centimeter of plasma is poured into each of six test tubes containing 0.3 cc. of isotonic solutions of Hoffmeister's reagents, (1) potassium sulphate, (2) potassium chloride, (3) potassium bromide, (4) potassium nitrate, (5) potassium iodide, and (6) potassium thiocyanate. The tubes are placed in a water bath at 50 C. and the temperature is gradually raised to 60 C. in thirty minutes. The number of tubes in which flocculation has occurred is then noted.

Darányi Test.—Two-tenths cubic centimeter of serum is added to 1.1 cc. of alcohol diluted with 2 per cent sodium chloride solution, shaken well and placed in a water bath at 60 C. for twenty minutes. The tubes are then placed at room temperature on a dark background and observed at one-half, one, two, three and twenty-four hours for signs of flocculation, which are expressed as + + + +, + + +, + +, +, or —. The alcoholic reagent is prepared by adding 4.1 cc. of freshly made 2 per cent sodium chloride to every cubic centimeter of 96 per cent alcohol. The exact amount of sodium chloride to be added is obtained by preliminary testing with serums of healthy controls.

Mátéfy Test.—Two-tenths cubic centimeter of serum is added to 1 cc. of 0.05 per cent aluminum sulphate solution, shaken once, placed at room temperature on a dark background and observed at one-quarter, one-half, and one and one-half hours for signs of flocculation. The results are read as + + + +, + + +, + +, + or — if there is no flocculation at the end of the one and one-half hour period.

Sedimentation Reaction (Morriss Modification).—Into a sterile 2 cc. Record syringe, a solution of 3.8 per cent sodium citrate is drawn up to the 0.4 mark. Blood is then aspirated from an arm vein to the 2 cc. mark, giving a dilution of 1:4. After thorough mixing, the citrated blood is poured into small Wassermann test tubes and taken to the laboratory where the blood is aspirated into long serologic pipets graduated into hundredths, placed in a rack and the layer of clear plasma observed at one, two and twenty-four hours and read directly in percentage. The two hour reading is the most significant one. The limits of normality are up to 5 per cent for men and 10 per cent for women.

We made the following minor changes from that given in the original articles. A 3.8 per cent sodium citrate solution was used instead of a 5 per cent strength for the sedimentation and plasma tests. Frisch and Starlinger's ± notation was omitted because of its unreliability in naturally opaque plasmas and also to make it easier for comparison with the other tests.

Our study comprises sixty-four cases, mainly surgical, including ten healthy controls (medical students). With few exceptions, the tests were run in duplicate and under as similar conditions regarding the time of day and meals as possible. The glassware was clean but not sterile and the tests not requiring water baths were carried out at a room temperature of from 20 to 25 C. For the comparison of the sedimentation, Frisch and Starlinger and Gerlóczy reactions, 8 cc. of venous blood was aspirated into a 10 cc. Record syringe containing 2 cc. of 3.8 per cent sodium citrate solution which gave the required 1:4 dilution. After two pipetfuls were removed for the sedimentation reaction, the remainder was centrifugated for one-half hour, the plasma decanted and used for the remaining tests. For the comparison of the sedimentation, Mátéfy and Darányi reactions, 10 cc. of blood were used of which 32 minims were removed for sedimentation, the remainder being allowed to clot overnight in an ice box and the serum thus obtained used for the other tests. For the comparison of all five tests, about 18 cc. of blood was used. The sedimentation pipets were placed in a specially constructed stand, the base of which was covered with a rubber mat, the pipets being firmly pressed against the mat by heavy elastic bands.

Before we proceeded with our tests, it seemed desirable to note the effect of the caliber of the pipets on the sedimentation speed. Repeated comparisons of 8 pipets ranging in lengths between 17.2 and 26 cm. gave differences at the end of two hours of about 2 per cent. The source of error due to small variations in pipets was therefore slight and became less with the use of pipets of more approximating sizes (from 19 to 21 cm.). This was corroborated subsequently by many duplicate sedimentation tests that were observed during the course of our experiments, the variations between readings averaging about 1 per cent, the greatest 3.5 per cent. Our results are in agreement with those of Horvat [6] and Berczeller and Wastl,[7] who found the longer and narrower tubes to give higher readings, and also with the observations of Westergren [8] and Fischel [9] to the effect that the height of the column is of more practical importance than the internal diameter of the tube.

Simultaneous comparisons were also made of the methods suggested by Peschel,[10] Morriss,[11] and Fischel [9] to determine if they could be compared on the percentage basis that the authors recommend.

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6. Horvat, A.: München. med. Wchnschr. **69**:1729, 1922.
7. Berczeller, L., and Wastl, H.: Biochem. Ztschr. **146**:370, 1924.
8. Westergren, A.: Klin. Wchnschr. **1**:1359 (July 1) 1922.
9. Fischel, K.: Am. Rev. Tuberc. **10**:606 (Jun.) 1925.
10. Peschel, G.: Beitr. z. Klin. d. Tuberk. **58**:195, 1924.
11. Morriss, W. H.: Am. Rev. Tuberc. **10**:431, 1924.

Tubes 1 and 2 of approximately the same length but of different diameters and volumes gave at two hours 27 and 25.5 per cent, respectively. This again indicates the importance of the height of column in contrast to lumen and volume. Tubes 2 and 3, each containing 2 cc. of blood, gave 25.5 and 35 per cent. It is therefore evident that the difference in length of the tubes is too great to give comparative values although there is a distinctly greater millimeter drop in tube 2. That this discrepancy is chiefly due to the length is shown by comparing tubes 3 and 6, which are of the same length but of different diameters and volumes; but that the volume is also a factor to be considered is seen from the higher reading in tube 5, which contains less blood. The sedimentation percentage in the Sahli hemoglobinometer tube (tube 4) was greater than in the others. It would seem, therefore, that with a constant quantity of blood small variations in the length and lumen of tubes of any given method can cause only slight degrees of error but that the comparison of methods which use pipets of wholly different

TABLE 1.—*Dog's Blood*

Experiment	Method	Volume, Cc.	Size Pipets	Sedimentation		
				1 Hour	2 Hours	24 Hours
1	Morriss.....	1.0	19.6 × 0.2 cm.	31 mm. 15.5%	54 mm. 27%	76 mm. 38%
2	Fischel.....	2.0	20 × 0.35 cm.	30 mm. 15%	51 mm. 25.5%	72 mm. 36%
3	Fischel.....	2.0	10 × 0.5 cm.	25 mm. 25%	35 mm. 35%	48 mm. 48%
4	Peschel (Sahli tube)	2.0	5.5 × 0.7 cm.	20 mm. 36%	25 mm. 46%	32 mm. 62%
5	Miscellaneous.....	1.2	10 × 0.4 cm.	26 mm. 26%	39 mm. 39%	52 mm. 52%
6	.....	2.3	10 × 0.55 cm.	23 mm. 23%	34 mm. 34%	48 mm. 48%

dimensions and volumes is not possible even on a percentage basis. We obtained similar results with the use of larger amounts of dog's blood as well as with human blood.

The simplicity of making readings directly in percentage without the use of a millimeter scale and time consuming interpolations makes the Morriss modification superior to the one suggested by Fischel; the blood column in the Sahli tube when filled to the 100 mark only reaches to about 5.5 cm. in height, and this short distance divided into 100 equal parts is a considerable source of error since the meniscus alone may involve several divisions.

The sedimentation, Frisch and Starlinger, and Gerlóczy reactions are arranged in table 2 to allow a better comparison of the results. It will be observed that with the exceptions of cases 12, 14, 20 and 22, there is a definite parallelism between sedimentation reaction and the heightened flocculating power of the plasma. The Frisch and Starlinger test is subject to individual interpretation and with naturally opaque plasmas this is a considerable source of error. The Gerlóczy test requires more time but the readings can be made more accurately than those of the Frisch and Starlinger test. By running double tests, a

TABLE 2.—*Comparison of Sedimentation, Frisch and Starlinger, and Gerlóczy Reactions* *

Experiment	Age	Sex	Clinical Diagnosis and Condition	Sedimentation, per Cent: 1 Hour	2 Hours	24 Hours	Frisch and Starlinger	Gerlóczy
1	22	♂	Medical student	1	1.5	17	−	+ − − − − −
2	23	♂	Medical student	1	2	25	−	+ ± − − − −
3	22	♂	Medical student	1	2	29	−	+ − − − − −
4	21	♂	Medical student	2	5	29	−	+ ± − − − −
5	62	♂	Hypertrophy of prostate; questionable renal stone	3.5	9	37	−	+ ± − − − −
6	15	♀	Chronic appendicitis, enteroptosis and congenital adhesions; appendectomy 8 days previously; T, P, R, normal	4	10.5	40	+	+ + − − − −
7	22	♀	Congenital adhesions; ptosis of cecum; exploratory laparotomy 13 days previously; T, P, R, normal	3.5	10.5	43	−	+ + − − − −
8	37	♂	Basal cell epithelioma of face 3 months after excision; T, P, R, nomal	4.5	11.5	37.5	−	+ ± − − − −
9	31	♀	Hypophyseal tumor; enucleation of adenoma of pituitary gland 2 months previously; T, P, R, normal	6	14	43	−	+ + ± − − −
10	28	♂	Osteomyelitis of left femur; removal of sequestrum and curettement 1 month previously; condition good	8	17	47	+	+ + ± − − −
11	36	♂	Tuberculosis of hip; Wassermann reaction, ++++; ankylosis of hip 6 weeks previously	8	19	44	+	+ + + + − −
12	70	♀	Fracture of neck of femur; plaster cast 5 months; T, P, R, normal	7	19	49.5	+++	+ + + + + +
13	56	♂	Emphysema and chronic bronchitis; moderate arteriosclerosis	9.5	21	48	++	+ + + + − −
14	32	♂	Duodenal ulcer; pyloroplasty 3 weeks later	12	26	53	+	+ + ± − − −
15	24	♀	Anal fissure; Wassermann reaction, ++++; T, 99.6	17	30	50	++	+ + + + ± −
16	21	♂	Clinical condition not diagnosed	21	37	59	++	+ + + + + ±
17	39	♀	Tuberculosis of spine; T, 99; plaster cast 2 weeks	20	38	63	++	+ + + + ± −
18	66	♂	Hypertrophy of prostate; perineal prostatectomy 9 days previously	22	38.5	60	++++	+ + + + + ±
19	61	♂	Acute appendicitis with abscess formation; operation 1 month previously; wound discharging	29	41.5	58	+++	+ + + + ± −
20	30	♀	Carcinoma of breast with metastases; radical operation 3 weeks previously	23	43	65.5	++	+ + + + + −
21	29	♂	Chronic empyema with discharging sinus; resection of four ribs 2 weeks previously	38.5	50	58	++++	+ + + + + +
22	28	♂	Deep abscess of thigh; two weeks after incision and drainage T, 100	35	55	67.5	++	+ + + + + ±
23	37	♂	Advanced pulmonary tuberculosis; T, 98.4; R, 20; P, 90; weight, 90 pounds (40.8 Kg.); sputum +; died 1 week later	48	56	62	++++	+ + + + + +
24	52	♂	Empyema of gallbladder; cholecystectomy and drainage 3 weeks previously; T, 101; P, 100	46	62	68	++++	+ + + + + +

* In this and the following tables, ♂ indicates male; ♀, female; T, temperature; P, pulse; and R, respiration.

finer differentiation could be obtained between the positive and the negative tubes. We also found it helpful to allow the tubes to stand overnight at room temperature and allow the diffuse precipitate to settle at the bottom. This checked our previous readings without seeming to affect the negative tubes. The Frisch and Starlinger test had to be read at the end of three minutes since the flocculation power of the plasma increased on standing. The four healthy controls and cases 6 and 7 gave readings within normal limits with the sedimentation reaction and, with one exception, with the Frisch and Starlinger test, but all gave + or + + with the Gerlóczy test, the latter finding being contrary to the results obtained by Gerlóczy who obtained no flocculation with normal plasmas. The sedimentation reaction gave no difficulty in setting up the pipets or in taking readings. The source of error of this test due to variations in the number and size of erythrocytes and the hemoglobin content will be discussed more fully later.

The Frisch and Starlinger test was found by its authors to parallel the sedimentation reaction and to depend primarily on the fibrinogen content of the plasma, a slight cloudiness or ± indicating less than 0.2 per cent and a strong flocculation or + + + +, more than 0.4 per cent fibrinogen. Deusch [12] found agreement between the sedimentation reaction, Frisch and Starlinger and the globulin content of the serum in cases of tuberculosis. This author also mentions the source of error due to the difficulty of interpretation of flocculation intensities. Weise,[13] on the basis of more than 2,000 tests on 500 tuberculous children and 150 adult women, recommends a combination of the sedimentation and Frisch and Starlinger tests in following the course of the disease. The relationship between the sedimentation, Frisch and Starlinger tests and his own test was noted by Gerlóczy. Torök [14] found the Gerlóczy reaction positive in tuberculosis and syphilis and negative in rickets, while parenteral infections caused less change in the colloid lability of the plasma of breast fed children than of those artificially fed. The Gerlóczy reaction was also noted in acute infectious diseases and tuberculosis by Cahn-Bronner.[15] In the cases of tuberculosis, it allowed prognostic decisions.

An excellent review of the sedimentation reaction and its applicability in tuberculosis is to be found in a recent monograph by Westergren.[16]

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12. Deusch, G.: Deutsche med. Wchnschr. **51**:229 (Feb. 6) 1925.
13. Weise, L.: Beitr. z. Klin. d. Tuberk. **56**:367, 1923-1924.
14. Torök, G.: Monatschr. f. Kinderh. **28**:14, 1923.
15. Cahn-Bronner: Verhandl. d. deutsch. Gesellsch. f. inn. Med., 36 Kong., 1924.
16. Westergren, A.: Ergebn. d. inn. Med. u. Kinderh. **26**:577, 1924.

Table 3 gives a comparison of the sedimentation, Mátéfy and Darányi reactions. In general, the Mátéfy reaction shows increased flocculation accompanying increased sedimentation but the results are not as marked as those obtained with the plasma tests. This is probably

TABLE 3.—*Comparison of Sedimentation, Mátéfy and Darányi Reactions*

Experiment	Age	Sex	Clinical Diagnosis and Condition	Sedimentation, per Cent: 1 Hour	2 Hours	24 Hours	Mátéfy	Darányi
25	22	♂	Medical student	1.5	3	17	—	—
26	24	♂	Medical student	1	3	25	—	—
27	26	♂	Medical students	2	5	35	—	—
28	23	♂	Medical student	5	12.5	36	—	—
29	18	♂	Deviation of nasal septum	2	7	36.5	—	—
30	37	♂	Basal cell carcinoma of face 4 months after operation; wound healed	4	8	31	+	—
31	17	♂	Fracture of fibula; T, P, R, normal	2	9	36.5	—	—
32	17	♀	Chronic constipation	4	9.5	39.5	+	—
33	61	♂	Cerebral arteriosclerosis (?); T, P, R, normal	3	10	39	—	—
34	22	♂	Tuberculosis of kidney; nephrectomy 4 months previously; T, P, R, normal; chest negative	4	10	40	—	—
35	20	♂	Crushing injury to great toe with gangrene of distal phalanx	4	10.5	36.5	++	—
36	52	♂	Hemorrhoids 20 days after operation	5	17	37	+	—
37	70	♂	Diverticulum of bladder; multiple renal calculi and left hydronephrosis	6	17.5	44.5	+	—
38	21	♂	Pilonidal sinus 2 weeks after excision	5.5	18	40	+	—
39	55	♂	Fistula of urethra and perineum 5 weeks after suprapubic cystotomy; T, P, R, normal	5.5	18	40	+	—
40	26	♂	Tuberculosis of hip; Wassermann reaction, ++++; ankylosis of hip 2 months previously	14.5	20	44	+	—
41	64	♂	Chronic osteomyelitis of femur and tibia 5 months after amputation of leg	12	21	41	++	—
42	31	♂	Acute appendicitis 11 days after appendectomy; T, P, R, normal	10.5	25	57	+	—
43	38	♀	Chronic appendicitis; adhesions about cecum 8 days after appendectomy	13	27	53.5	+	—
44	49	♂	Renal stone; removed 8 days later; died of pneumonia 2 weeks after operation	11	31	51	+	—
45	30	♂	Cervical lymphadenopathy, probably Hodgkin's; T, P, R, normal	15	31	56	++	—
46	46	♂	Tuberculous peritonitis; 18 days after exploratory laparotomy, slight afternoon temperature	20	36	62	++	—
47	73	♀	Fracture of femur; 3 weeks after immobilization	21.5	37.5	63	++	—
48	53	♀	Recurrent spindle cell sarcoma of buttock; operation 1 year previously	27	41	62	++	—
49	29	♂	Chronic empyema with discharging sinus; 5 weeks after resection of 4 ribs, T, P, R, normal	36.5	44	52	++++	—
50	18	♀	Acute appendicitis; 3 days after appendectomy T, 100, P, 100	27	45	62	++	—
51	28	♂	Deep abscess of thigh; 1 month after incision and drainage, T, 100, P, 100	40	49	62	+++	—
52	52	♂	Empyema of gallbladder; cholecystectomy 5 weeks previously; drainage; slight temperature	35	57.5	66	++	—
53	57	♂	Carcinoma of stomach with metastases; T, 100	45.5	59	68	+++	—

owing to the fact that the plasma tests include the most labile component, the fibrinogen, as pointed out by Sachs and von Oettingen [17] whereas the serum reactions depend on an increased globulin-albumin ratio.

17. Sachs, H., and von Oettingen, K.: München. med. Wchnschr. **68**:351 (March 25) 1921.

The Darányi reaction was found negative in all the cases studied; the serums on removal from the water bath showed various degrees of opalescence but no definite flocculation.

Diverse results have been obtained with the Mátéfy reaction by different investigators. Some of the discrepancies are due to the difficulty of making accurate readings while others are due to the uncertainty of the test to indicate tissue destruction in pathologic conditions and the frequency of positive reactions in healthy controls. Krömeke [18] corroborated Mátéfy's findings in tuberculosis and found the reaction positive in syphilis, malignant tumors and in other processes accompanied by cell destruction, while healthy individuals or those with superficial catarrhal processes gave negative results. Lukács [19] obtained + and + + flocculations among healthy children and although + + + and + + + + readings were found in tuberculosis, syphilis, acute infections and chronic inflammations, the test lost much of its value since only the two higher gradations were of any significance. Poor results with the Mátéfy reaction were reported by Basch,[20] who found no relationship between the test and the extent of the disease process or the degree of activity. Winkler and Gerth [21] obtained negative reactions in 10 per cent of active tuberculous cases and positive ones in 25 per cent of healthy controls, while Beekmann [22] and Büttner [23] noted positive reactions in about one-half their healthy controls. The sedimentation reaction permitted a better follow-up of the therapeutic effects on the tuberculous process. The sedimentation reaction is recommended by Zwerg [24] as a much simpler and more reliable test than the Mátéfy reaction. Gaehtgens and Gockel [25] compared the sedimentation with the Mátéfy reaction on 187 adults with tuberculosis and found the Mátéfy reaction frequently positive in inactive and negative in active cases. Positive sedimentation reactions were of considerable value in prognosis as well as in diagnosis when other conditions giving positive reactions could be excluded but a negative outcome did not exclude an active tuberculosis.

The difficulty of interpreting flocculation intensities even after stated time intervals accounts to a greater extent for the difference in the results reviewed. Our own observations agree more with those of Zwerg since we had only one + + + + and four + + + reactions in forty observations, but we did not obtain any positive reactions with serums of

18. Krömeke, F.: Deutsche med. Wchnschr. **50**:231 (Feb. 22) 1924.
19. Von Lukács, J.: Med. Klin. **20**:788 (June 8) 1924.
20. Basch, F.: Med. Klin. **20**:384 (March 23) 1924.
21. Winkler, W., and Gerth, H.: Med. Klin. **20**:1080 (Aug. 3) 1924.
22. Beekmann, A.: Deutsche med. Wchnschr. **50**:1537 (Nov. 7) 1924.
23. Büttner, H. E.: München. med. Wchnschr. **72**:50 (Jan. 9) 1925.
24. Zwerg, H.: Deutsche med. Wchnschr. **51**:353 (Feb. 27) 1925.
25. Gaehtgens, W., and Gockel, M.: Beitr. z. Klin. d. Tuberk. **59**:36, 1924.

healthy controls. We were able to differentiate in the Mátéfy reaction two forms of flocculation; one manifested itself by a diffuse finely dispersed, granular turbidity which settled slowly to the bottom. Such flocculations frequently accompanied high sedimentation values. The reaction was called positive when the floccules had settled sufficiently to show a clear zone of serum above. This usually took from twenty to thirty minutes or + + +. Centrifugating a few specimens verified our interpretation. The second form of flocculation was observed in serums of low flocculating power. In these cases, large, uneven flakes were observable at the bottom of the test tube in from one to one and one-half hours in a previously clear or slightly turbid serum. Normal serums showed flocculations in from two to three hours.

The Darányi [26] reaction was noted by its originator to coincide to some extent with the sedimentation reaction and the increased precipitation of plasma and serum by various methods, all being measures of tissue destruction. His results have been corroborated by Duzár [27] in tuberculous children. Kremer [28] found several cases of 102 studied which did not show flocculation but in general the reaction coincided with the stage of the disease, being weakly positive in the first and second stages and strongly positive in the third stage. The Darányi reaction was obtained by Krömeke [29] in the primary and secondary stages of syphilis; but in eighty-two cases of uncomplicated, latent or congenital, seropositive syphilis it was negative, indicating little toxic formation in the organism. Kruchen [30] used the Darányi reaction in 300 cases of tuberculosis and in 200 it was compared with the sedimentation reaction. In 23 per cent, the Darányi reaction gave wrong results and, because of the insufficient number of gradations, he did not find the test as practical as the sedimentation reaction, although in the latter he found the red blood cells to be a factor. Nassau and Hendelsohn [31] obtained positive reactions in acute intestinal intoxications in children. Sauvan and Chiappe [32] noted the reaction in only two conditions, in sixty-four cases of tuberculosis and in ten of cancer. In all other conditions, including pneumonia, pleurisy, typhoid, malaria and syphilis, the test always was negative. These authors believe the test can be used in differential diagnoses in these two conditions. Mendel [33] obtained positive reactions in other diseases besides tuberculosis, while

26. Von Darányi, J.: Wien. klin. Wchnschr. **35**:885 (Nov. 9) 1922.
27. Duzár, J.: Jahrb. f. Kinderh. **102**:69 (May) 1923.
28. Kremer, W.: Ztschr. f. Tuberk. **38**:428, 1923.
29. Krömeke, F.: Med. Klin. **19**:310, 1923.
30. Kruchen, C.: Beitr. z. Klin. d. Tuberk. **58**:301, 1924.
31. Nassau, E., and Hendelsohn, W.: Klin. Wchnschr. **2**:1835 (Oct. 1) 1923.
32. Sauvan, A., and Chiappe, X.: Compt. rend. Soc. de Biol. **90**: 1265, 1267 (May 16) 1924.
33. Mendel, L.: Jahrb. f. Kinderh. **106**:15 (May) 1924.

Steinbrinck [34] prefers the use of plasma for the testing of colloid lability because serum lacks the most labile component, fibrinogen.

From the review of some of the conflicting results that have been obtained with the Darányi reaction and from our own observations, it would appear that the test, in its present condition, is not suited for the determination of tissue destruction. It is also obvious that a test that tends to become more positive in conditions of cachexia cannot be of much help in the early diagnosis of disease even if it were to possess specificity. For the same reason it loses in value as a finer indicator of tissue destruction. From the recent work of Furth and Bluh [35] and Dalla Volta and Benedetti,[36] it seems that when minute amounts of alcohol are added to serum, marked changes are produced in the physicochemical structure of the latter and these observations are confirmed clinically by Rusznyak, Barat and Kurthy,[37] who believe that the Darányi reaction does not depend on the amount of globulin but that it is a manifestation of hitherto unrecognized changes in the serum. The problem requires more study.

The mechanical difficulties are greater with the Darányi than with the other reactions. It is necessary to titrate accurately the amount of 2 per cent sodium chloride solution to be added to the alcohol reagent by preliminary testing of the serums of healthy controls. Darányi used 4.1 cc.: 1cc. of 96 per cent alcohol solution. We used 4.2 cc.: 1 cc. of 96 per cent alcohol solution but only three of six serums of healthy controls showed any consistency in the flocculation with the different concentrations.

Table 4 is a comparative study of all five tests. The results agree with those tabulated previously with the exception of cases 60 and 61, which gave a negative, and case 64 which gave a ++ Mátéfy reaction in the presence of marked increases in the sedimentation, Frisch and Starlinger and Gerlóczy reactions. Duzár and Rusznyak [38] studied the colloid lability of infant's blood by means of the sedimentation, Frisch and Starlinger, Gerlóczy and Darányi reactions as well as the total proteins, albumin, globulin and fibrinogen fractions and found the first three tests to run parallel while the Darányi test was frequently negative when the others were positive. The plasma tests were found related to the fibrinogen and the Darányi test to the globulin fractions.

The theories that have been advanced in explanation of the sedimentation reaction are intimately related with those suggested for the

34. Steinbrinck, W.: Ztschr. f. klin. Med. **100**:39 (May) 1924.
35. Furth, R., and Bluh, O.: Kolloid. Ztschr. **34**:129, 1924; Phys. Abstracts **9**:287, 1924.
36. Dalla Volta, A., and Benedetti, P.: Arch. di. sc. biol. **5**:287, 1923-1924; Physiological Abstr. **9**:421, 1924.
37. St. Rusznyak; Barat, L., and Kurthy, L.: Klin. Wchnschr. **2**:1479, 1923.
38. Duzár, J., and St. Rusznyak: Monatschr. f. Kinderh. **28**:25, 1923.

plasma and serum flocculation tests although the presence of red blood cells in the former complicates matters. In the case of the sedimentation reaction it is generally assumed that there is an increased agglutination of the red blood cells in rapidly sedimenting bloods, the larger clumps tending to settle more quickly to the bottom. But whether the increased agglutination is primarily due to a change in electric potential

TABLE 4.—*Comparison of Five Tests*

Experiment	Age	Sex	Clinical Diagnosis and Condition	Sedimentation, per Cent: 1 Hr.	2 Hr.	24 Hr.	Frisch and Starlinger	Gerlóczy	Mátéfy	Darányi
54	21	♂	Medical student	1	2	23	—	+ ± — — — —	—	—
55	26	♂	Medical student	1	2.5	24	—	+ — — — — —	—	—
56	23	♂	Dislocation of semilunar cartilage of knee; T, P, R, normal	2	5	21	—	+ ± — — — —	—	—
57	36	♂	Tuberculosis of hip; Wassermann reaction ++++; ankylosis of hip 3 months previously	14	20	40	+	+ ± — — — —	+	—
58	42	♂	Chronic osteomyelitis of femur of 13 years' duration; 7 weeks after curetting and insertion of drains wound still discharging	10	20	41	++	+ + + — — —	++	—
59	19	♂	One day after removal of adenoids and tonsils, T, 99.6; P, 90	19	34	52	++	+ + ± — — —	++	—
60	62	♂	Lacerations about head following accident; T, 100; P, 90	22	37	54	++	+ + ± — — —	—	—
61	41	♂	Clinical condition not diagnosed; abdominal and gastric symptoms; red blood cells, 2,860,000; hemoglobin, 50% (Talquist); roentgen-ray examination showed a questionable duodenal ulcer	28	48	62	+++	+ + + ± — —	—	—
62	36	♂	Multiple fractures 2 months after admission; wounds almost healed; T, P, R, normal; Wassermann reaction ++++	40	52	63	++++	+ + + + + ±	+++	—
63	25	♂	Pilonidal sinus 1 day after excision and curettage; T, 99.6; P, 100	43	55	64	++++	+ + + + + +	+++	—
64	31	♂	Maxillary sinusitis; T, 100; P, 90; toxic symptoms	45	60	66	++++	+ + + + + +	++	—

between negatively charged erythrocytes and positively charged bodies in the plasma (Fahraeus-Höber theory [39]) or whether it is due to an increase in the fibrinogen fraction of the plasma (Frisch and Starlinger theory [40]) is still debatable. Chemical studies have shown that the sedimentation reaction is accompanied by an increase in the globulin

39. Höber, R., and Mond, R.: Klin. Wchnschr. **1**:2412 (Dec. 2) 1922.
40. Frisch, A., and Starlinger, W.: Med. Klin. **17**:1147; 1177, 1921.

albumin ratio,[41] and this factor is considered the basis of the serum flocculation tests. Others have shown an increase in fibrinogen [42] and this factor is the basis of the plasma flocculation tests. Still others have demonstrated increases in viscosity [43] cholesterin,[44] phosphorus [45] and lipase [46] which accompany these colloid lability reactions. It would seem, therefore, that with our present knowledge no single component of the blood can be held accountable for the phenomena observed but that these reactions express the total of complicated physicochemical changes that accompany disease, and various factors may play a rôle in their causation, depending on the nature, location and severity of the disease process.

The influence of the number and size of erythrocytes and their hemoglobin content on the sedimentation reaction has been the primary cause for the advocacy of testing plasma and serum instead. Bürker [47] and his pupils found that the size and hemoglobin content of the erythrocytes influenced sedimentation. Behrens [48] and Bönniger and Herrmann [49] also are of the same opinion. The latter corroborated Abderhalden's [50] findings, that the various layers of red blood cells have different sedimenting properties. The question is not of great moment. On another occasion we made over 100 complete blood counts in conjunction with the sedimentation reaction and found no relation between the number and hemoglobin content of the red blood cells and the sedimentation reaction. The counts were not of cases of anemia or polycythemia and averaged between four and five and one-half millions of erythrocytes and from 70 to 80 per cent hemoglobin (Sahli method). Between such limits the red blood cell factor was of no appreciable importance. It is well known that a marked diminution of erythrocytes causes an acceleration while an abnormal increase causes a delay in the sedimentation reaction, but in such instances the blood picture would probably be of greater clinical significance than the colloid lability tests that have been suggested. Opitz

41. Salomon, A.: Ztschr. f. klin. Med. **99**:329, 1924.

42. Seki, T.: Biochem. Ztschr. **143**:365, 1923. Murakami, J., and Yamaguchi, T.: Ann. de med. **15**:297 (April) 1924. Schindera, M.: Deutsches Arch. f. klin. Med. **144**:113 (May) 1924.

43. Petschacher, L.: Ztschr. f. d. ges. Tuberk. **20**:284, 1923.

44. Kürten, H.: Klin. Wchnschr. **3**:1216 (July 1) 1924. Lasch, F.: Ztschr. f. d. ges. exper. Med. **42**:548, 1924. Grossmann, H.: Ztschr. f. d. ges. exper. Med. **42**:496, 1924.

45. Stern, A.: Deutsches Gesell. f. Kinderh. **9**, 1924.

46. Lederer, M.: Monatschr. f. Kinderh. **27**:608 (March) 1924.

47. Bürker, K.: München. med. Wchnschr. **69**:577, 1922.

48. Behrens, B.: München. med. Wchnschr. **71**:229 (Feb. 22) 1924.

49. Bönniger, M., and Herrmann, W.: Klin. Wchnschr. **3**:403 (March 4) 1924.

50. Abderhalden, E.: Arch. f. d. ges. Physiol. **193**:236, 1921-1922.

and Frei [51] have shown that in children, only in anemia is there found with regularity any relationship between the sedimentation reaction and the color index of the red blood cells but that in individuals with a normal blood status, the sedimentation reaction is seldom influenced by this factor. Similar opinions are held by others.

CONCLUSIONS

1. Depending on the toxicity of a disease process, a proportional increase in the erythrocyte sedimentation reaction and the ability of flocculation of the plasma and serum, as determined by the Frisch and Starlinger, Gerlóczy and Mátéfy reactions, was found. The Darányi reaction was negative in forty cases studied.

2. Because of its greater simplicity, accuracy and wider range of readings the sedimentation reaction seemed the most practical test to use clinically. A percentage basis suggested by Morriss offered a convenient method of noting the results.

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51. Opitz, H., and Frei, M.: Jahrb. f. Kinderh. **100**:55, 1923.

THE SEASONAL VARIATION IN THE ONSET OF ACUTE DIABETES

THE AGE AND SEX FACTORS IN 1,000 DIABETIC PATIENTS*

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It is evident to those who see a considerable number of patients with diabetes that, if the disease is classified according to its actual onset, two main forms are encountered. One form begins acutely and is ushered in with the abrupt appearance of the symptoms familiar to every physician. The course is usually downward; this form usually attacks persons less than 40. The other may be so gradual in onset and course in some instances that it is impossible to determine the date of origin. The presence of sugar in the urine is discovered quite by accident. Diabetes which comes on insidiously is ordinarily associated with obesity and arteriosclerosis.

In taking the history of patients with acute diabetes, when the date of onset can be fixed with reasonable certainty, I was impressed by the fact that there are certain seasons of the year when the onset of the disease is more common. With the idea of confirming this impression, the case records of 1,000 patients with diabetes were studied. In this group there were 317 cases that could be classified as acute and in which the disease began so suddenly that there could be no question as to the time. Case records were discarded when there was any question about this point. In examining these records, I was constantly mindful of the possibility that a mild chronic case of diabetes might suddenly become more severe from some cause and the usual symptoms of diabetes not be forcibly brought to the patient's attention until then.

The results of classifying the cases according to the month of onset of disease are shown (fig. 1). It appears that acute diabetes is most likely to be precipitated during the fall, winter and spring.

Seventy-seven and three-tenths per cent of the patients studied came from Minnesota, Montana, Michigan, Nebraska, the Dakotas, Iowa, Wisconsin, northern Illinois and central southern Canada. The possible relationship between the onset of acute respiratory infections and the onset of the diabetes is obvious. The states mentioned have a long winter season, and the inhabitants are therefore exposed to longer seasons when colds in the head, acute bronchitis, influenza and the like are prevalent. Often a patient said that his diabetes appeared immediately after such an infection and in most cases a history of preceding infection was obtained, although, in many it was thought too trivial to

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require a physician. In some cases the diabetes started abruptly without a preceding infection. It is probable, however, that a disproportionate number of these patients had not observed their condition carefully.

A long winter season forces many persons to lead sedentary lives and it is doubtful whether they deliberately eat less because they are less active. Therefore, a possible sequence of events is as follows: one person, on account of heredity or other reasons, may be slightly more susceptible to diabetes than another. During a period of enforced idleness he eats as much food as during his period of activity. He develops an acute respiratory infection. This combination of events is sufficient to throw the balance in favor of diabetes. It is interesting in this connection to note that for 1922 the death rate from diabetes for the reported northern states was considerably greater than for the reported southern states. To quote the twenty-third annual report of the department of commerce:

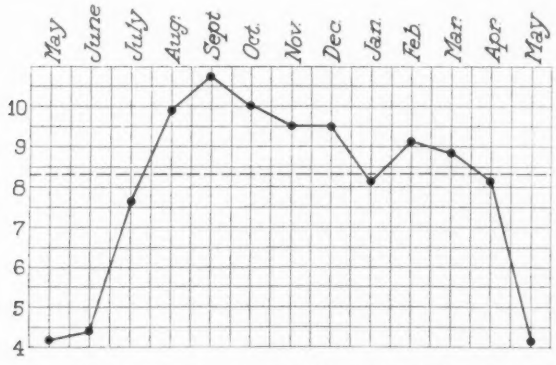

Chart 1.—Percentage of 317 cases of acute diabetes according to month of onset.

The states with the highest death rate from diabetes in 1922 are New Hampshire (31.1 per hundred thousand), Vermont (27), New York (26.9), Maine (25.3), and those with the lowest rates are Mississippi (7.3), South Carolina (7.6), Tennessee (7.7), Kentucky (8.1), and North Carolina (8.7).

If one divides the United States at 37 degrees latitude he finds that the states above the line have a diabetic death rate of 19.3 per hundred thousand and the states below a death rate of 8.5. It might be asserted that this discrepancy is due to the greater reliability of the mortality statistics of the northern states, but I cannot believe that this accounts for it entirely.

Seventy per cent of the diabetic patients coming to the clinic live in towns of 10,000 population or less. Thirty-one per cent live in places of less than 1,000 population (table 1). Whether all our patients developed diabetes in these environs cannot be determined. They probably did not. However, considerably more than half of all the patients

coming to the Mayo Clinic live in rural districts. This fact makes enforced idleness during the winter months seem the more likely.

In order to discover at what time of life a person is most likely to develop diabetes, a series of 1,000 patients of all types was studied with reference to their age at the time the disease was discovered. Included in this group of patients are a number with the onset of the diabetes not accurately fixed. This applies particularly to older patients. Nearly

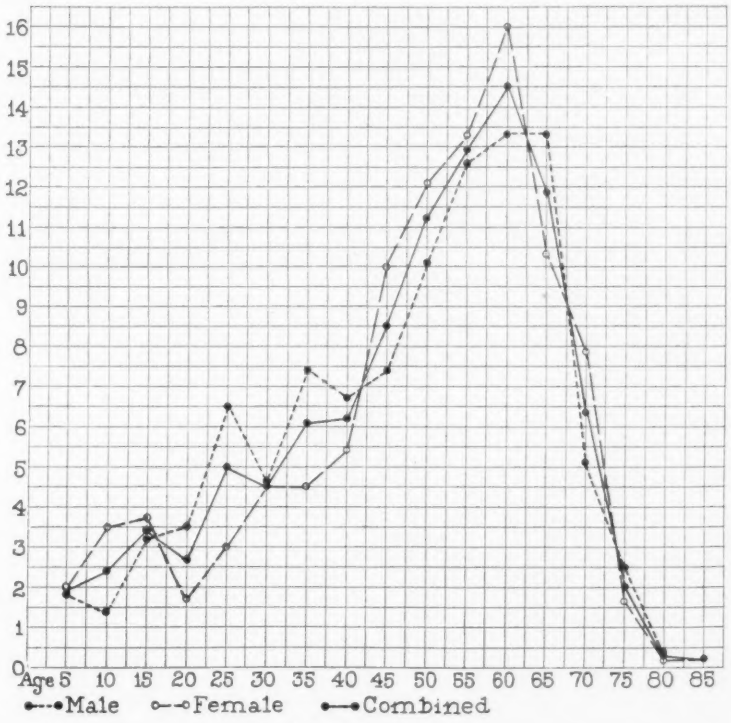

Chart 2.—Percentage of 1,000 cases of diabetes at various ages.

every patient, however, was able to tell at least at what age his diabetes was discovered.

In charting these according to half decades (fig. 2), it appears that there is a gradual increase in diabetes with increase in age, in a population largely rural, up to the age of 60. Beyond this point there is an acute decline in the incidence.

The data reveal that 593 of the 1,000 developed diabetes after the age of 45. The percentage of diabetes in patients more than any given age is noted in table 2.

The sex distribution in the 1,000 patients under consideration for all ages was 58 per cent males and 42 per cent females.

SUMMARY

Diabetes of the acute progressive form, as seen in the middle west, is a disease that begins more frequently in the fall, winter and spring than in the summer. A more sedentary life and a greater incidence of acute respiratory infections during this period suggest a combination of circumstances favorable for the precipitation of diabetes. Diabetes is

TABLE 1.—*One Thousand Diabetic Cases Grouped According to Size of Town*

Size of Towns	Cases
1 to 1,000	326
1,000 to 2,500	185
2,500 to 10,000	172
10,000 to 100,000	196
Above 100,000	121
Total	1,000

TABLE 2.—*Age Incidence*

Years	Males		Females		Total
	Cases	Per Cent	Cases	Per Cent	Per Cent
1- 5	10	1.8	9	2.0	1.9
6-10	9	1.4	15	3.5	2.4
11-15	18	3.2	16	3.7	3.4
16-20	20	3.5	7	1.7	2.7
21-25	37	6.5	13	3.0	5.0
26-30	26	4.6	19	4.5	4.5
31-35	42	7.4	19	4.5	6.1
36-40	39	6.8	23	5.4	6.2
41-45	42	7.4	43	10.0	8.5
46-50	60	10.1	52	12.1	11.2
51-55	72	12.6	57	13.3	12.9
56-60	76	13.3	69	16.0	14.5
61-65	75	13.3	44	10.3	11.9
66-70	29	5.1	34	7.9	6.3
71-75	14	2.5	7	1.6	2.0
76-80	2	0.4	1	0.2	0.3
81-85	...	...	1	0.2	0.2
Total	571		429		

	Per Cent
Total patients more than 10 years of age	95.7
Total patients more than 20 years of age	89.6
Total patients more than 30 years of age	80.1
Total patients more than 40 years of age	67.8
Total patients more than 50 years of age	48.1

a disease that gradually increases in incidence with age up to 60, after which there is a sudden decline in frequency, due probably to the falling off of the population of persons over 60. It is slightly more prone to afflict males than females. The figures here reported are based on studies of diabetes as seen in the middle west. General conclusions, however, should not be drawn from the study of patients from one section of the country. Only by combining observations made in different sections of the country can any real estimate of facts be properly made.

Book Reviews

INTRODUCTION TO DERMATOLOGY. By SIR NORMAN WALKER. Eighth Edition. New York: William Wood & Co., 1925.

This new edition of Sir Norman Walker's Introduction to Dermatology should be a welcome addition to every practitioner's library. Like its predecessors it is a book that is a pleasure to read. It is written in an easy, intelligible style and gives the reader a clear conception of the commoner skin conditions.

Many additions have been made to the last edition. The text is well illustrated with photographs and colored plates and the print is large and easily read. It sums up in a clear concise manner the teachings of the Edinburgh school and should be read by every physician interested in dermatology

SCIENTIFIC REPORTS FROM THE GOVERNMENT INSTITUTE FOR INFECTIOUS DISEASES, TOKIO IMPERIAL UNIVERSITY. Director, MATARO NAGAYO. Edited by YONEJI MIYIGAWA. Vol. III. Tokyo: Shirokane-Daimachi, 1924.

This volume covers a wide range of activities, including bacteriology, chemistry and pathology, and the imposing character of the work reported cannot fail to impress one with the great importance of this research institute. The present report contains nineteen articles covering 241 pages, with profuse illustrations. Many of these papers are simply résumés of one or more far more elaborate articles originally published only in Japanese. Here all are translated into English or German, with one in French.

Of special note is the summary of the research by a number of workers on tsutsugamushi disease. By intradermal inoculation of blood from infected patients they have reproduced the disease typically. The causative organism is proved to be nonfiltrable and nonculturable on all ordinary mediums. It can be transmitted only by the bite of a small mite, *Trombicula akamushi*. The offending organism is multiform, having monococcal, diplococcal and bacillary forms, and cannot as yet be classified zoologically. However, it bears a striking resemblance to the microcorpuscles of *Rickettsia*, although the latter is borne by a blood sucking parasite and *Trombicula* is lymph sucking.

Special mention may also be made of the paper by Ikeda showing that the immunity transmitted from mother to young is not transmitted through the placenta but through the milk in the first few days of life. The immunizing substances are not destroyed by the gastric juice of the new-born. Miyagawa and Kada's demonstration of the influence of the thymus on growth also is important. They show that small doses of thymus administered parenterally cause a remarkable increase in growth in young animals but that larger ones are toxic and retard growth. This explains many of the discrepancies in the literature.

Most of the work reported is of a high grade of importance, but space will not permit even a summary of what is already largely a condensation of far more detailed reports.

TROUBLES DE LA FONCTION GASTRIGUE ET SYNDROMES ASSOCIÉS CHEZ LES TUBERCULEUX PULMONAIRES (LA TOUX EMÉTISANTE). By PIERRE MARSAL. Inaugural thesis at the University of Nancy. Paris: A. Maloine et fils.

This thesis is the report of a careful, thorough study of sixty-five cases in the sanatorium at Nancy in the service of Parisot. All of these were active cases of pulmonary tuberculosis that presented grave gastric symptoms. Digestive disturbances occurred in 20 per cent of all consumptives and were about

three times as common in women as in men. While fundamentally these troubles are due to the toxemia of the infection they are often brought on by overfeeding and medication. Many closed cases had gastric disturbances, showing that swallowed septic matter was not necessarily a factor.

Examination of the stomach did not as a rule show any extreme degrees of variation from the normal. In the early cases there was a hypersecretion and a hyperactivity of the gastric juices as shown by digestive tests. Roentgenoscopy generally showed a hypermotility and a marked tendency to spasm. Later in the course of the disease both the gastric motility and the secretory functions appear slightly diminished. Late cases coming to postmortem examination confirmed this picture. The mucosa was slightly atrophied and there was a subacute interstitial gastritis of low grade; this was in all probability due to swallowed septic matter, although no actual tubercles or evidences of tuberculosis of the stomach were encountered.

In the foregoing class of cases there was definite evidence of a vagotonia, which, however, was not the underlying cause. In another category, that of the postprandial vomiting, the factor of the vegetative nervous system was predominant. This syndrome occurred in 23 per cent of Marsat's cases. It is variously described as a deglutition cough, Morton's cough or vomiting cough (toux émétisante). The cough is undoubtedly brought on by deglutition; this cough is of such violence that vomiting is induced. Nausea is generally absent. Fundamentally the vegetative nervous system is at fault. It is an exaggeration of perfectly normal reflexes. The sensory arc of these reflexes is the vagus and the motor arc is the phrenic nerve through the superior cervical ganglion. The hypersensitive sensory arc is stimulated by swallowing, which brings on the cough; when the patient is out of breath and inspires deeply and suddenly there is a contraction of the diaphragm and abdominal walls accompanied by a negative pressure in the chest. The hypertonic stomach at this moment tends to empty itself into the esophagus.

In the therapeutics of this condition atropine has given excellent results.

THE PATHOLOGY OF TUMORS. By E. H. KETTLE, M.D., B.S., London. Second Edition. New York: Paul B. Hoeber, 1925.

As stated in the preface, the plan of this book is to provide a manual for students that will contain the generally accepted teaching on the pathology of tumors without the mass of detail necessary in a larger work of reference.

The author has no doubt succeeded in doing this and the book will serve a real need in the presentation of this subject to students, especially in primary and optional courses in pathology. For a work of this kind the illustrations are satisfactory and are relatively numerous.

There are short chapters on the etiology of cancer and on the experimental study of cancer, but most of the book is given over to the classification of tumors and a description of the standard types. Ofter these descriptions are so terse that they are of little or no value.

There is a brief presentation of the work of Peyton Rous and of Gye on the possible existence of an infecting virus. Apparently the monumental work of Maude Slye on the relation of heredity to cancer has been overlooked.

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